FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

Acthar Gel (NDA 22-432) Background Package

May 6, 2010

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

The Inn and Conference Center, University of Maryland University College (UMUC)
Marriott Conference Centers
3501 University Boulevard East, Adelphi, MD

QUESTIONS TO THE ADVISORY COMMITTEE

MAY 6, 2010

1. Substantial evidence of effectiveness can consist of data from adequate and well-controlled clinical investigations (replication) or a single adequate and well controlled clinical investigation and confirmatory evidence.

    a. Has the sponsor provided substantial evidence of effectiveness for Acthar Gel as a treatment for patients with Infantile Spasms (IS)? **[Voting Question]**

    b. If so, which standard described above has been met?

2. If the answer to Question 1 is yes, has effectiveness been shown in: 1) cessation of spasms, 2) amelioration of the EEG, 3) prevention of other seizure types, 4) improvement in long-term developmental outcomes, or 5) other outcomes?

3. If the answer to Question 2 is no, what additional data should be obtained prior to approval?

4. The sponsor wishes to recommend a 2 week course of treatment, followed by a 2 week tapering regimen. Has the sponsor submitted evidence to support the view that a short course of treatment provides sustained effectiveness? **[Voting Question]**

5. If the answer to Question 4 is no, can you provide dosing recommendations (for example, is there evidence that continued treatment beyond 2 weeks is appropriate, or is there evidence that repeated, intermittent short courses of treatment are useful)?

6. Acthar Gel has been shown to cause serious adverse effects, and the sponsor concludes that they are predictable, easily recognized and manageable, and reversible upon drug discontinuation.

Has the sponsor provided evidence that the adverse events are manageable and reversible? **[Voting Question]**

7. Has the sponsor submitted sufficient evidence of the safety of Acthar Gel at an effective dosing regimen? **[Voting Question]**

8. If the answer to Question 7 is no, what additional safety data should be obtained prior to approval?

9. Are there patients in whom Acthar Gel should be contraindicated (e.g., infants with hypertension, infections, or metabolic disorders)?

10. Does the committee recommend any specific monitoring for specific adverse events?

    If so, should these be made mandatory under a REMS?

MEMORANDUM

DATE: April 5, 2010

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: Members
Peripheral and Central Nervous Systems Advisory Committee
(PCNS AC)

SUBJECT: Memo to PCNS AC Members for May 6, 2010 meeting to discuss NDA 22-432, for the use of H.P. Acthar Gel (repository corticotrophin injection) in the treatment of Infantile Spasms (IS)

As you know, there will be a meeting of the PCNS AC on May 6, 2010, to discuss NDA 22-432, for the use of H.P. Acthar Gel (repository corticotrophin injection) in the treatment of Infantile Spasms (IS). Though not approved for the treatment of IS (Acthar Gel was approved in 1952 and has been approved subsequently for numerous indications), Acthar Gel has been the treatment of choice for IS for many years. This NDA supplement was submitted by Questcor Pharmaceuticals on 6/23/06. The Agency issued a Not Approvable (NA) letter on 5/10/07. Subsequent to the NA letter, the company and the Division of Neurology Products (DNP) entered into discussions about how this indication could be pursued. The sponsor had not conducted any trials of its own, and, in brief, we determined that the sponsor should attempt to obtain primary data for several trials published in the archival literature that, potentially, could provide substantial evidence of effectiveness for Acthar Gel for IS. The sponsor obtained data from three of these studies, as well as safety data from various sources. With these data, the sponsor has submitted a response to the CR letter on 12/10/09.

This briefing package contains reviews by Dr. Philip Sheridan, medical officer in the Division of Neurology Products (DNP), who has reviewed the effectiveness and safety data, and Dr. Jialu Zhang, statistician, who has reviewed the effectiveness data. In addition, we are including copies of five articles from the literature: The three articles that describe the controlled trials for which the sponsor obtained the primary data, a Practice Parameter from the American Academy of Neurology and the Child Neurology Society, published in Neurology, 2004, discussing treatment options for IS, and an article by Partikian and Mitchell, published in the Journal of Child Neurology, 2007, describing safety experience in a cohort of patients with IS, for which the sponsor also obtained the primary data and which constitutes a significant portion of the sponsor's submitted safety data. Finally, we are enclosing the list of questions we would like you to discuss at the AC meeting in May.

In this memo, I will briefly review the effectiveness and safety data, and discuss those issues (and provide the specific questions) that we would like the committee to discuss and/or vote on at the 5/6/10 meeting.

Effectiveness

As noted above, the sponsor has submitted data from three controlled studies that they believe provide substantial evidence of effectiveness for Acthar Gel as a treatment for IS.

Study 01

This was a single blind, parallel group study in which patients with IS were randomized to receive either ACTH 150 Units/meter^2/day given as a 75 Unit/meter^2 dose twice a day or prednisone 2 mg/kg/day (in a 1 mg/kg BID regimen) for 2 weeks. Each treatment was tapered to 0 over the subsequent 2 weeks. This study was performed by Dr. Baram in 1996.

The primary outcome was based on a video EEG performed at 2 weeks; the video EEG was to be for 24 hours, but in all cases was to be at least 4 hours (to include a full sleep-wake cycle). An Overall Success was defined as a patient who experienced no spasms and elimination of hypsarrythmia, the characteristic EEG pattern in these patients. The investigator did not pre-specify primary or secondary outcomes; the outcome described here was chosen by the sponsor and represents the widely accepted definition of clinical success by the expert community. Seizure frequency was also monitored and recorded by the patient's caregiver during the 2 weeks of the study.

The treating physician was not blinded to treatment assignment, but the video-EEGs were read by a blinded rater.

Results

A total of 15 patients were randomized to receive ACTH, and 14 were randomized to receive prednisone. About 86% of each group had symptomatic IS and about 14% had cryptogenic IS. The mean age was about 5-7 months old.

A total of 13/15 (87%) of ACTH patients were classified as an Overall Success compared to 4/14 (29%) of prednisone patients (p=0.0025, according to Dr. Zhang). An examination of the proportion of patients who met criteria for an EEG response revealed 13/15 (87%) ACTH patients compared to 4/14 (29%) prednisone patients (p=0.0025), and 14/15 (93%) of ACTH patients and 4/14 (29%) of prednisone patients met clinical success criteria (p=0.0005).

According to the sponsor, of the 13 patients who originally responded to ACTH, 2 relapsed. Of the 11 remaining infants who had responded, 3 had no recurrence

(though they were only followed for a month), and 8 were reported to have had no recurrences, after having been followed for at least 6 months (mean 17 months). Presumably, recurrences were based on caretaker reports.

Study 05

This study compared a high dose of ACTH to a low dose.

In this study (performed by Dr. Hrachovy in 1994), patients received ACTH at 150 Units/meter^2 (HD) given once a day or ACTH 20 Units/day (LD**)**, both given IM. The HD was given for 3 weeks, followed by a 9 week taper, and the LD was given for 2 weeks followed by a 2 week taper.

As in Study 01, the primary outcome was complete cessation of spasms and complete resolution of the EEG pattern on video EEG. In the HD group, the video EEG was performed at Week 12, after the taper period. In the LD group, the video EEG was performed at the end of the initial 2 week treatment period. If patients did not respond in the HD group, they were treated with prednisone, 2 mg/kg/day for 4-6 weeks, and then followed in a "routine clinical manner". If patients in the LD group did not respond at 2 weeks, their ACTH dose was increased to 30 Units/day for an additional 4 weeks, and then tapered over a 2 week period.

Results

A total of 59 patients were randomized to treatment (the current sponsor was able to obtain original data for 58).

A total of 30 patients were randomized to HD and 29 to LD. Four (4) HD patients did not complete the study, compared to 5 LD patients. The sponsor analyzed the following populations:

Modified intent-to-treat (mITT): Patients who received at least one dose of drug and had adequate data to assess the overall response.

Intent-to-treat: All patients randomized.

Spasms Population: All patients with "sufficient" data to evaluate the complete spasm response. Presumably, "sufficient" data meant any data collected on this outcome; there need not have been EEG data to be included in this population.

Completed Patients: All patients who completed the study in the opinion of the investigator

The following outcomes were assessed:

Overall Response: Any patient who had complete cessation of spasms and resolution of the EEG at any time during the study

Spasm Control Response: Any patient who had completed cessation of spasms at any time during the study. This included all patients with cessation of spasms during treatment or follow-up as assessed by clinical observation or parental report.

Hypsarrhythmic EEG Pattern Response: Any patient who had resolution of the EEG pattern at any time during the study.

The median age was 6.7 months old.

The following table displays the results of the various outcomes in the several populations.

Pop.	Treatment	Overall Response	Spasm Control	EEG Response
mITT	HD	15/24 (63%)	19/24 (79%)	16/24 (67%)
	LD	13/27 (48%)	14/27 (52%	14/27 (52%)
P-value		0.28	0.03	0.27
ITT	HD	15/30 (50%)	23/30 (77%)	16/30 (53%)
	LD	15/29 (52%)	16/29 (55%)	13/29 (45%)
P-value		0.94	0.07	0.52
Spasm	HD	15/28 (54%)	23/28 (82%)	16/28 (57%)
	LD	13/27 (48%)	14/27 (52%)	14/27 (52%)
P-value		0.64	0.013	0.66
Completed	HD	15/26 (58%)	21/26 (81%)	16/26 (62%)
	LD	13/24 (54%)	14/24 (58%)	14/24 (58%)
P-value		0.82	0.08	0.83

A total of 3/15 (20%) of HD and 2/13 (15%) of LD patients relapsed (these are patients who met the Overall response criteria at some point, but later were noted to have failed these criteria, based on video EEG verification performed based on caretaker reports of recurrent spasms).

Study 04

This was a double-blind, randomized trial comparing ACTH and prednisone. The study was performed by Dr. Hrachovy in 1983.

In this study, patients were randomized to receive ACTH 20 Units/day IM and prednisone placebo or ACTH placebo and prednisone 2 mg/kg/day PO for 2 weeks.

If the patient responded to the drug (same responder definition as in the previous studies) at 2 weeks, the drug was tapered over 1-2 weeks. These patients were monitored at 2 and 6 weeks after the end of the taper period. If the patient did not respond in the first 2 weeks, they continued the original treatment for 4 weeks. If they did not respond during this 4 week period they were switched to the other drug after a one week washout. If they did respond after the 4 week period, they had drug tapered over 1-2 weeks.

Results

A total of 24 patients were randomized, 12 to each group.

The median age was 8.2 months. Similar outcomes (Overall Response, Spasm Response, and EEG Response) were analyzed.

The following table displays the results for the initial phase of the study, presumably meaning the first 2 weeks.

Treatment	Overall	Spasm	EEG
ACTH	5/12 (42%)	5/12 (42%)	9/12 (75%)
Prednisone	4/12 (33%)	4/12 (33%)	4/12 (33%)
P-value (for the Overall Variable)	0.99	0.99	0.99

Safety

The sponsor obtained analyzable safety data from 3 sources:

A retrospective chart review performed by Partikian and Mitchell (N=84).

Another retrospective chart review from 4 clinical sites (N=178).

Safety data from Study 05 (N=57).

Together, these sources provide safety data from a total of 319 patients.

Drs. Partikian and Mitchell reviewed charts from all patients treated for IS (in patient and out-patient) at the Children's Hospital of Los Angeles (CHLA) between January 1996 and August 2006. These patients were treated with a standard protocol: ACTH 150 Units/meter^2/day (given as a BID regimen) for 1-2 weeks, followed by a taper of 4-5 weeks.

Patients were evaluated at all visits from 1-3 weeks after treatment initiation, at 4-8 weeks after treatment initiation, and at 3 months or more after treatment initiation. Assessments included adverse events reported by caregivers, weight and blood pressure, medication changes and the development of new seizure types.

As noted above, a total of 84 patients received initial treatment of ACTH in this cohort.

As noted by Dr. Sheridan, common adverse events included irritability, increased appetite, infections, and difficulty sleeping. These were mostly reported during the first follow-up visit, and decreased as drug was tapered.

Serious adverse events included seizures (not known if this represented new seizure types or exacerbation of IS), infections, and hospitalizations.

Mean changes in weight of 11%, 18%, and 26% were seen at the first, second, and third follow-ups, respectively. As Dr. Sheridan notes, it is difficult to know if this weight gain was related to ACTH or growth of the patient over time.

At baseline, 18% of patients had at least one significant increase in systolic blood pressure (SBP), compared to 33% at the first follow-up. The percent of patients who had at least one significant increase in SBP was 21% and 4% at the second and third visits, respectively.

At baseline, 14% of patients had at least one significant increase in diastolic blood pressure (DBP), compared to 24%, 11%, and 5% at the first, second, and third follow-up, respectively.

The second study involved retrospective chart review at 4 clinical centers, covering a period from January 2000 to May 2008. These patients received ACTH in a range of 135-160 Units/meter^2/day in a BID regimen (Questcor Recommended Dose); > 80 Units/meter^2/day but outside the recommended range, or within the recommended range, but once a day (Other high dose); or <80 Units/meter^2/day (Low dose). Adverse events were assessed at baseline, subsequent visits, and a final visit (any visit at least 2 weeks after the last dose of ACTH).

As noted above, data on 178 patients was collected.

A total of 59% of patients had at least one adverse event. In the Recommended and Other high dose groups, 62% and 64%, respectively, had at least one AE compared to a rate of 30% in the Low dose group. The most common AEs in the Recommended dose group were hypertension (18%), irritability (12%) and left ventricular hypertrophy (8%). In the Other high dose group, Cushingoid appearance (13%) and increased appetite (11%) were also seen.

A total of 20 patients had at least one Serious AE (SAE). A total of 10 patients had an SAE of hypertension (most recovered with specific treatment of drug discontinuation), 5 patients had infections (mostly pneumonia), and there was one case each of hepatomegaly, fever, respiratory failure, diarrhea, reflux, convulsion, hypertrophic cardiomyopathy, and renal failure.

There was one death, due to aspiration pneumonia.

Other common adverse events included upper gastrointestinal irritability, infections, drowsiness, sleep difficulties, fever, and increased secretions.

There were reversible blood pressure increases that returned to baseline with discontinuation of treatment.

Study 05

This was the study that compared the 150 Units/meter^2/day given as a single IM dose for 3 weeks followed by a 9 week taper compared to a 2 week dose of 20 Units/day or additional treatment for 4 weeks with 30 Units/day in non-responders.

There were a total of 57 patients in this study; 93% in the high dose and 86% of the patients in the low dose had at least one adverse event. The most common adverse events and clinical findings are given below:

Event	High dose	Low dose

Candidiasis	36%	38%
Cushingoid	29%	21%
Otitis media	25%	21%
Irritability	14%	17%
Fever	18%	14%
Acne	21%	10%
Diarrhea	21%	7%
Increased BP	18%	7%
Vomiting	11%	10%
Drowsiness	18%	10%
Sleep difficulties	46%	35%
Increased appetite	50%	24%
Decreased appetite	43%	31%

One child, a 3 month old boy with multiple medical problems, developed pulmonary edema, respiratory failure, and died of cardiac arrest after several weeks of treatment (20 Units-40 Units/day).

Serious AEs in the high dose group (N=4 patients) were dehydration, pneumonia, increased blood pressure, decreased appetite, and skin discoloration.

Four (4) patients (1 high dose, 3 low dose) discontinued treatment due to adverse events. These events included high blood pressure, skin discoloration, fever, and otitis media.

Across all 319 patients, 134 were dosed with the Recommended Dose, 133 with the Other High Dose, and 52 with the Low Dose. Across these dose groups, the adverse event pattern reflects, of course, the types and incidences of events seen in the individual studies (see Dr. Sheridan's review, page 42, which reprints the sponsor's table of the common AEs across doses); there is no obvious dose response for any given adverse event. The most common AEs are infections, irritability, Cushingoid appearance, and hypertension.

Post-Marketing reports

The sponsor has presented reports of adverse events from the spontaneous reporting system from 1952 to June 2009. The sponsor identified AEs in patients treated for IS or in infants between 1-24 months. Of course, we do not have information on how many patients have been treated for this indication or in this age group.

There were a total of 76 reports meeting these criteria, with 33 considered serious. Dr. Sheridan describes these events; they are mostly similar to those events already described.

Discussion

The sponsor has submitted data from three controlled trials that they believe provide substantial evidence of effectiveness for Acthar Gel as a treatment for patients with IS. In addition, they have provided safety data from 319 patients treated with Acthar Gel, under various treatment conditions, with 134 treated at the recommended dose (75 Units/meter^2/day BID), and another 135 treated at doses close to that, but given once a day.

The data that the sponsor has provided differ considerably from that typically submitted in an NDA. As noted earlier, none of the studies were commissioned or conducted by the sponsor, and detailed protocols, and, in particular, detailed statistical plans for the analyses of these studies, did not exist. The sponsor has presented the results of these studies in a uniform way; that is, the primary outcome in each trial (Overall Response) was taken to be the same, and mirrored the expectations of the expert community regarding an effective treatment for IS; namely, complete cessation of spasms and normalization of the typical EEG pattern. The sponsor presents one of the studies, Study 01, as the "pivotal" study, one of the studies, Study 05, as a "supportive" study, and Study 04 as an "additional" study.

Although Study 01 did not, apparently, have a detailed statistical plan, the results showed a clear (nominally) statistically significant superiority to prednisone not only on the overall response, but on the individual components (EEG and spasms). This result occurred with a total sample size of only 29 patients. This result has been confirmed by the Agency's statistician, based on her review of the primary data that the sponsor obtained from the investigator.

The results of Study 05 are more difficult to interpret. There were no differences between the Overall Response Rates in the high and low dose groups (and the treatment paradigms were different in the two groups), and the only (nominally) statistically significant differences were seen in the Spasm Control variable, with nominal p-values varying between 0.01 and 0.08, depending upon the population analyzed.

The third study, Study 04, was of a complicated design, making interpretation difficult. In any event, no differences were seen between the two treatment groups (ACTH and prednisone).

Study 01 lends itself to a fairly straightforward interpretation, but this seems not to be the case for the other two studies. Dr. Sheridan does point out that the response rates, though basically not different between the treatment groups in these 2 latter studies, do seem to be greater than published estimates of the placebo response rates (he cites a placebo response rate of about 5% for a study by Appleton, et al., a study previously relied upon, to some extent, by the Agency when we considered the approval of Sabril for IS). However, it is fair to

say that the interpretation of an active control trial that does not demonstrate a difference between treatments (the case for these latter two studies) is problematic, at best.

The Food, Drug, and Cosmetic Act requires that the Agency find that a sponsor has submitted substantial evidence of effectiveness (in addition to adequate safety) in order to approve a New Drug Application. Substantial evidence of effectiveness is defined as data from adequate and well-controlled clinical investigations (typically interpreted to mean more than one such trial) or data from a single such trial and confirmatory evidence (neither the circumstances under which this latter standard should apply nor what constitutes "confirmatory evidence" is defined in the Act). As a general matter, this latter standard is applied in the setting of a serious or life-threatening condition in which a second trial is essentially impossible to perform (for any of a number of reasons), and a wide variety of evidence can be considered "confirmatory" (e.g., a very low p-value, multiple sub-groups and or study sites strongly positive, multiple outcomes strongly positive, etc.). However, whether to apply this latter standard to any given data set, and what constitutes confirmatory evidence, are issues that are open for discussion. We will be asking you to decide whether or not the statutory standard for substantial evidence of effectiveness has been met in this application, and, if you believe it has, which of the standards described above has been met.

With regard to the question of effectiveness, there is another important question we would like you to address. As you know, ACTH has been the standard of care for patients with IS for many years. The typical treatment course consists of a short (e.g., two weeks) period of treatment, followed by a tapering period. If patients experience a recurrence of spasms, another short course is given. It has long been considered that such short courses are all that is necessary to control the spasms after the treatment is discontinued. If you conclude that the treatment is effective, we will be asking you whether or not you can conclude that the data presented support the sustained effectiveness of the treatment after discontinuation.

The sponsor has also submitted safety data of the sort that is not typically contained in an NDA. Specifically, a typical NDA contains complete reports of a cohort of patients prospectively followed forward in time. This permits a complete (or near complete) accounting of the experience of all patients started on a particular treatment (e.g., how many patients discontinued, what all of the adverse events were, etc.). That is not the case here.

As described, much of the data presented has been obtained from a retrospective review of charts of patients treated with ACTH at various institutions over the course of several years. The data were not collected for the purpose of establishing the safety of the treatment, as would be the case in typical company-sponsored drug trials. The adverse events described are, for the most part,

those known to be associated with treatment with ACTH. We will be asking you if you can conclude that these data, both in terms of the numbers of patients treated at the recommended doses (or those similar to, or greater than, the recommended doses), as well as in terms of the completeness of the data collected, support a conclusion that the safety of the treatment has been adequately determined.

As mentioned at the beginning of this memo, we have included in this package the specific list of questions we would like you to address at the meeting on May 6th. We have noted which ones we would like you to provide a formal vote on, as well as those we are interested in hearing your comments on. Of course, we are eager to hear if you believe there are any other issues that you feel are important to consider that we have not raised.

I thank you in advance for the work you will do in preparation for the meeting, and for your work at the meeting. I look forward to seeing you all on the 6th.

References

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Hrachovy RA, Frost JD Jr, Glaze DG. High-dose, long-duration versus low-dose, short duration corticotropin therapy for infantile spasms. J Pediatr. 1994 May;124(5 Pt 1):803-806.

Mackay MT, Weiss SK, Adams-Webber T, Ashwal S, Stephens D, Ballaban-Gill K, et al. American Academy of Neurology; Child Neurology Society. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology. 2004 May 25;62(10):1668 1681.

Partikian A, Mitchell WG. Major adverse events associated with treatment of infantile spasms. J Child Neurol. 2007 Dec;22(12):1360-1366.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022432
Priority or Standard	P
Submit Date(s)	December 10, 2009
Received Date(s)	December 10, 2009
PDUFA Goal Date	June 10, 2010
Division / Office	Division of Neurology Products, ODE-1
Reviewer Name(s)	Philip H. Sheridan, M.D.
Review Completion Date	March 31, 2010
Established Name	Repository Corticotropin
Trade Name	Acthar Gel
Applicant	Questcor Pharmaceuticals
Formulation(s)	For Intramuscular Injection
Dosing Regimen	BID
Indication(s)	Infantile Spasms
Intended Population(s)	Pediatric

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

Pending following Advisory Committee May 6, 2010

2 Introduction and Regulatory Background

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Acthar Gel was approved in 1952 and was successively owned by several companies including Armour Pharmaceutical Company, Rhone-Poulenc Rorer, and Aventis. Aventis was formed by the merger of Rhone-Poulenc Rorer with Hoechst AG.

In 2001, Questcor purchased the marketing rights to Acthar from Aventis. Since that time, with active collaboration with the Food and Drug Administration (FDA), Questcor has been working to submit a Supplemental New Drug Application (sNDA) that would support the approval of Acthar for the treatment of patients with IS.

Questcor received a Complete Response letter to its sNDA submission with specific deficiencies in May 2007. In a subsequent Type C Meeting with FDA on November 9, 2007, Questcor was encouraged to do the following, where possible: 1. Obtain the source data from the 5 published, randomized control studies where Acthar was evaluated for the treatment of patients with IS and perform independent analyses of the data (Askalan 2003, Baram 1996; Dreifuss 1986; Hrachovy 1994; Hrachovy 1983); 2. Obtain source data from hospitals that had treated patients in the last 10 years and then to perform its own independent safety analyses of these data. 3. Provide FDA with safety on enough IS patients treated with Acthar to define the safety profile in these patients and to assert that the benefit outweighs the risk.

Following this meeting, Questcor attempted to obtain data from the 5 RCTs, and was successful in obtaining data from 3 of those 5 studies (Baram 1996, Hrachovy 1994, Hrachovy 1983). Data for the other 2 RCTs were no longer available due to the age of those studies. In addition, Questcor obtained data from a safety study conducted in 2007 (Partikian 2007) and also conducted its own retrospective chart review protocol to obtain source safety data from IS patients treated at 4 hospitals.

2.6 Other Relevant Background Information

Not applicable

3 Submission Quality and Integrity

3.1 Submission Quality and Integrity

As discussed in detail in this review, the three studies presented in support of efficacy and the four studies presented in suport of safety do not meet usual Agency standards for approval. The Sponsor has shown due diligence in obtaining the most complete data available and in presenting them with scientific integrity.

Efficacy Data Quality:

Most NDA submissions provide efficacy data collected prospectively using prespecified protocol and comprehensive patient data collection forms from a double blinded randomized study of the NDA study drug versus a control (placebo or active control). Because the studies supporting this NDA were done as small academic studies and not intended to support an NDA submission, this quality of efficacy data is not available. Furthermore, there was no formal follow-on protocol after the pivotal efficacy study or after the supportive efficacy study that could provide a reliable relapse rate for all responders over a 6 month or greater time period. Longer-term data concerning neurodevelopment or the later appearance of other forms of epilepsy among the responders are not available.

A complete prospective protocol, comprehensive patient data collection forms, and prespecified statistical analysis plan were not available.

Safety Data Quality:

Most NDA submissions provide safety data collected prospectively using prespecified protocol and comprehensive patient data collection forms from a double blinded randomized study of the NDA study drug versus a control (placebo or active control). Because the studies supporting this NDA were done as academic studies and not intended to support an NDA submission, this quality of safety data is not available. The safety data presented was compiled retrospectively in an unblinded fashion from the charts of patients who had participated in academic randomized clinical studies or who were treated for infantile spasms independent of a randomized trial at an academic center. The data available in the charts was not collected according to predetermined prospective protocol and patient data collection forms. Thus, the data is prone to be incomplete. The patient charts from the pivotal efficacy study were not available to the Sponsor so this study did not directly contribute any safety data.

This safety information is supplemented by adverse event reports submitted to the Sponsor and by a survey of adverse events attributed to Acthar Gel in the published

literature. These are useful in screening for adverse effects observed in the larger treatment population (beyond the safety studies used in this submission) that were not identified in the relatively small number of study patients receiving Acthar Gel (319 patients in 3 safety studies). However, the likelihood of an observed adverse effect being reported from this larger population is unknown making the numerator of an estimated incidence of an observed adverse effect uncertain. Furthermore, the size of this larger treatment population is not known so there is also no denominator for estimating incidence of adverse effects observed.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Not applicable

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Efficacy Studies	Title
CSR 222017-01	Pivotal Efficacy Study: High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study (Baram, 1996)
CSR 222017-05	Supportive Efficacy Study: High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms (Hrachovy, 1994)
CSR 222017-04	Additional Data for Efficacy: High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms, A Prospective, Randomized, Blinded Study (Hrachovy, 1983)

Safety Studies	Description	Number of Acthar Gel-treated patients contributed to Integrated Safety Tables
CSR 222017-02	Partikian and Mitchell retrospective chart review	84
CSR QSC007-ACT-002	Questcor retrospective chart review at 4 sites	178
CSR 222017-05	Hrachovy 1994 Study of Acthar Gel High vs Low Dose (charts reviewed retrospectively for safety data)	57
CSR 222017-04	Hrachovy 1983 study of ACTH vs Prednisone (patients on Acthar gel not identifiable in retrospective chart review)	None
Total Patients in Integrated Safety Tables	See section 7.2.1 of this review	**319**

5.2 Review Strategy

I have reviewed the individual clinical study reports and the integrated summaries of efficacy and safety for the efficacy and safety studies. I have also reviewed the published articles from the three efficacy studies and from the Partikian safety study, and I have compared them to the corresponding clinical study reports.
Questcor obtained source efficacy data from the study conducted by Dr. Baram (Baram 1996). Questcor's analyses of these data are presented as CSR 222017-01. CSR 222017-01 is presented as the pivotal efficacy study.

Questcor also obtained source efficacy data from the 2 additional RCTs conducted and published by Dr. Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983). Questcor's independent analyses of these data are presented as CSR 222017-05 and CSR 222017-04, respectively.

CSR 222017-05 is presented as the supportive efficacy study. Additional efficacy data supporting the use of Acthar for the treatment of IS patients is presented in CSR 222017-04.

All three studies assessed the efficacy of Acthar Gel by the combined primary endpoint of cessation of spasms (determined by video EEG sessions) and the elimination of the hypsarrhythmia.

The safety data submitted in this Complete Response comes from the independent analyses of the data obtained in studies conducted by Drs. Partikian and Mitchell (CSR 222017-02) which presumably included safety data from CSR 222017-01 not otherwise available, the Questcor Retrospective Study (CSR QSC007-ACT-002), and the studies conducted by Hrachovy and colleagues (CSR 222017-05 and CSR 222017-04), together with the data in the Questcor postmarketing surveillance safety database and the published literature

5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor presents three individual studies in support of efficacy in this NDA submission:

Pivotal Study for Efficacy CSR 222017-01 (Baram, 1996)

The pivotal study was entitled, "High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study". It compared Acthar 150 U/m2/day administered as 75 U/m2/bid IM for 2 weeks with a taper to zero for an additional 2 weeks and prednisone 2 mg/kg/day administered as 1 mg/kg/bid orally (PO) for 2 weeks with a taper to zero over 2 weeks in patients with IS.

The patients were assessed for both the elimination of clinical spasms as well as a remission of hypsarrhythmic EEG pattern characteristically seen in these patients.

Reviewer's Note:
This combined endpoint (elimination of spasms and of hypsarrhythmia) is generally recognized as the most clinically meaningful endpoint for efficacy studies of infantile spasms. Unlike the efficacy success of treatments of other seizure types where reduced seizure frequency is significant, success for efficacy studies of infantile spasms is an "all-or-none" phenomenon.

The use of video-EEG for assessment of spasms elimination and the elimination of hypsarrhythmia is also essential to a good infantile spasms study. Even experienced clinicians may miss subtle spasms (undercount) or mistake a nonepileptic infantile movement for a spasm (overcount) without a simultaneous EEG tracing for detection or confirmation. Video EEG also allows for a blinded

EEG interpreter who does not know to which arm of the study an infant is assigned to determine if the infant's response satisfies the primary endpoint.

This study is considered single blind because the infants were not subjected to a "double-dummy" study where twice-daily sham injections would be given to infants randomized to oral prednisone. However, given that an infant would not be expected to associate one treatment over the other with likely improvement in its condition (or even associate the experience of being treated with any expected benefit) and that the endpoint is objective rather than subjective, it is unlikely that a placebo response affected the outcome. Thus, the study almost can be considered "double-blind".

Dr. Baram and her colleagues had previously published the study results from their analyses of the data (Baram 1996). Questcor obtained the primary efficacy data from the investigators and, with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-01.

Reviewer Note:

The data available from Dr. Baram was largely limited to her published article (1996) and her spreadsheet of patients. Regrettably, the safety data was not available to Questcor. It is presumed that the 15 patients initially randomized to Acthar Gel are included in the patients who were retrospectively studied by Partikian (See section 7.1.1 of this review). However, none of the patients are definitely identifiable as being from the Baram study.

Design: Patients eligible for enrollment into this study were diagnosed with clinical IS, defined according to Jeavons (1964). An infant previously treated with any steroid or Acthar treatment was not eligible for the study. Informed consent was obtained from each patient's parent or guardian. All patients had a 24-hour video-EEG to ascertain the presence of hypsarrhythmia before initiation of treatment. Seizure frequency was monitored throughout the 2-week treatment period by parents who maintained seizure diaries. After 2 weeks of treatment, a repeat video-EEG was performed, and both clinical and EEG responses were assessed by a blinded EEG interpreter. Video-EEG monitoring was performed for a minimum of 4 hours and, optimally, for 24 hours, always including a full sleep wake cycle.

Reviewer Note:
It is important that at least one full sleep-wake cycle be observed since the incidence of infantile spasms varies during the cycle. It would be cleaner if all infants had a 24 hour post-treatment video EEG. From available data, It cannot be determined an equal number of the less than 24 hour video EEG sessions occurred in each arm of the study. However, given the "all-or-none" nature of a

positive response to infantile spasm therapy, this flaw is probably less significant than it might be in a study of another seizure type.

Adverse events such as hypertension and hyperglycemia were monitored; urine specimens were checked for glucose throughout the duration of treatment, and blood pressure was measured biweekly. The safety results were not included in the published article (Baram, 1996) and were not available for Questcor to include in the clinical study report.

Acthar 150 U/m2/day was administered as 75 U/m2/bid IM for 2 weeks and then tapered to zero for an additional 2 weeks. Prednisone 2 mg/kg/day was administered as 1 mg/kg/bid PO for 2 weeks, and then tapered to zero over 2 weeks. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment.

Video-EEG was used to establish response to treatment. For a patient to be considered an Overall Responder to treatment, both of the following had to occur: remission of clinical spasms and a resolution of the characteristic pattern of hypsarrhythmia on EEG. Electrographic response consisted of resolution of the hypsarrhythmic pattern on both sleep and wake EEG. The emergence of background slowing or other epileptiform patterns was considered a positive response

Efficacy Findings

Results: Thirty-six (36) patients met clinical and EEG criteria for entry into the study. Two (2) were ineligible for treatment, 1 had severe hypertension and 1 experienced resolution of spasms after shunt placement. Thirty-four (34) patients were, therefore, eligible to enroll in the study.

Twenty-nine (29) of the 34 eligible infants with clinical IS were enrolled in the study; the 5 who were not enrolled were due to parental refusal (2), unavailability of legal guardian (2), and other issues (1).

Fifteen (15) patients were randomized to Acthar and 14 patients were randomized to prednisone. Twenty-five (25) patients (25/29, 86.2%) had symptomatic etiology of IS and 4 patients (4/29, 13.8%) had cryptogenic etiology of IS. No stratification was done prior to randomization, but 2 cryptogenic patients were randomized to each arm.

Reviewer Note:
The older medical literature suggests that cryptogenic patients may respond more often than symptomatic patients. The published article (Baram, 1996) notes that, given modern neuroimaging and other diagnostic testing, the cryptogenic category is smaller than in older reports. In this small study, there was no

significant difference in response between cryptogenic and symptomatic patients.

The Questcor analysis of the efficacy data of CSR 222017-01 demonstrated the following:

- The combined clinical endpoint of spasm cessation combined with cessation of the hypsarrhythmic EEG indicated greater efficacy of Acthar (13/15, 86.7%) compared to prednisone (4/14, 28.6%), P=0.0015.
- The differences between Acthar and prednisone for the separate EEG and clinical response of spasm cessation were statistically significant (P=0.0015 and P=0.0003, respectively) favoring the Acthar treatment group. Electroencephalogram response was 86.7% for Acthar and 28.6% for prednisone. Corresponding clinical response rates for spasm cessation were 93.3% and 28.6%, respectively.
- Age distributions appeared to be slightly different between the treatment groups, but these differences were not statistically significant.
- Adjusting for age group the secondary analyses confirmed that differences between Acthar and prednisone for the combined clinical endpoint and for the separate EEG and clinical spasms responses remained statistically significant (P<0.01, for any age grouping).
- One (1) of 2 patients (1/2, 50%) crossed-over to prednisone responded by both EEG and clinical criteria. Seven (7) of 8 patients (7/8, 87.5%) with data available documenting cross-over to Acthar responded by both EEG and clinical spasm criteria.

Reviewer Note: The published article indicates that 2 patients relapsed of the 14 responding to ACTHAR originally (15% rate). The period of follow-up is not specified.

Questcor Conclusions: This study demonstrated that Acthar 150 U/m2/day administered as 75 U/m2/bid IM was superior to prednisone 1 mg/kg/bid PO for elimination of clinical spasms and hypsarrhythmia in patients with IS using a 2-week high-dose regimen with a 2-week taper. This Acthar regimen was superior to prednisone when analyzing the overall response endpoint (combined measure of cessation of spasms and eliminating the hypsarrhythmia on EEG) (the more definitive measure of treatment success) as well as in the individual measurements of spasm cessation and elimination of the hypsarrhythmic EEG pattern.

Reviewer Note: All but one of the patients who responded with cessation of spasms also showed disappearance of hypsarrhythmia. The fact that this one patient was on Acthar Gel rather than prednisone is not likely to be significant since there were many more patients with cessation of spasms on Acthar gel (14/15) than on prednisone (4/14).

Supportive Efficacy Study: CSR 222017-05 (Hrachovy 1994)

The supportive efficacy study CSR 222017-05 was entitled, "High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms," a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen to Acthar low-dose regimen in patients with IS.

The Acthar high-dose regimen consisted of Acthar given at a dose of 150 U/m2/day as a single (150 U/m2/QD) IM dose for 3 weeks followed by a 9-week taper; the Acthar low-dose regimen consisted of Acthar 20 U/day (20 U/QD) as a single IM dose for 2 weeks followed by a 2-week taper in responders or a dose escalation to 30 U/QD IM in nonresponders.
The principal investigator, Dr. Hrachovy, and his colleagues had previously published the study results from their analyses of the data (Hrachovy 1994). Questcor obtained the primary efficacy data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-05.

Reviewer Note:
Unfortunately, although the "high dose" of 150 U/m2/day is the same total daily dose used in the pivotal study (CSR 222017-01, Baram), this "supportive efficacy study" gave the injection once daily rather than dividing the injection BID. The BID dosage is believed to increase the cortisol response which may be related to the mechanism of action for causing cessation of spasms. Also, the high dose is given for 3 weeks and tapered for 9 weeks but the CSR 222017-01 pivotal study gave the high dose for 2 weeks and tapered for 2 weeks. Furthermore, the different timing of the EEG between the two arms of the study makes this study difficult to interpret.

Study Design: Patients enrolled in the study were diagnosed with IS defined by both the presence of clinical spasms and a hypsarrhythmic EEG pattern. All study participants were under the age of 4 years, had onset of spasms prior to the age of 12 months, and continued to have spasms at the time of entry into the study. Patients who had previously received ACTH or corticosteroid therapy for their spasms were not eligible for the study.

Informed consent was obtained from each patient's parent or guardian. Prior to the initiation of treatment, patients were monitored using a video-EEG for up to 24 hours in order to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored with video-EEGs 2 to 3 times during the treatment period; the treatment period was 12 weeks for the high-dose and 6 weeks for low-dose. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the

start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150 U/m2/QD had been administered. Patients were evaluated throughout the study for spasm cessation and safety.

Treatment Protocol: Eligible patients were first stratified as having either cryptogenic or symptomatic IS and then randomized to receive treatment with either high-dose Acthar (150 U/m2/QD IM for 3 weeks, followed by 80 U/m2/QD IM for 2 weeks, then 80 U/m2/every other day [QOD] IM for 3 weeks, then 50 U/m2/qod IM for 1 week, and then Acthar was tapered to zero over 3 weeks) or Acthar low-dose (20 U/QD IM for 2 weeks). Nonresponders to the high-dose Acthar regimen were treated with prednisone 2 mg/kg/day PO for 4 to 6 weeks, and then followed in a routine clinical manner. Nonresponders to low-dose Acthar had their Acthar increased to 30 U/QD for an additional 4 weeks followed by a taper to zero over a 2-week period.

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report.

Efficacy Measures: The primary efficacy endpoint was the Overall Response. An Overall Response was defined as both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study. The secondary efficacy endpoints were the assessment of efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

Reviewer Note:
The stratification of cryptogenic vs. symptomatic IS is a good feature of this study which the pivotal study (CSR 222017-01, Baram) did not have. Some reports in the literature suggest that infants with cryptogenic IS have a better initial response overall prognosis.

The length of the video EEG sessions varied. The sponsor does not have records of how long each session was or whether one arm of the study might have averaged longer sessions than the other arm.

There were 4 efficacy analysis populations for this study. These were defined as follows:

- Modified Intent-to-Treat Population: The modified Intent-to-treat (mITT)Population, the primary efficacy population, included all patients who were randomized, received ≥ 1 dose of Acthar study medication, and had sufficient data to evaluate the Overall Response.

- Intent-to-Treat Population: The Intent-to-treat (ITT) Population included all patients randomized to treatment. A sensitivity analysis of treatment efficacy was performed using the ITT Population.

- Spasms Population: The Spasms Population included all patients with sufficient data to evaluate the Spasm Control Response.

- Completed Patients Population: The Completed Patients Population included all patients in the study who completed the treatment with Acthar as designed by the protocol (i.e., were not prematurely withdrawn from the study), and were judged to have completed the protocol by the investigator.

The analysis of treatment response was performed in each of the 4 efficacy populations for each of the 3 responder groups:

- Overall Responders,
- Spasm Control Responders, and
- Hypsarrhythmic EEG Pattern Responders.

Each patient was classified as a Responder or Nonresponder for the determination of Overall Response (i.e., spasm cessation combined with resolution of the hypsarrhythmic EEG pattern), as well as for the determination of Spasm Control Response alone and Hypsarrhythmic EEG Pattern Response alone based on data collected to the Treatment Response case report form page as explained below:

- Overall Response: Overall Responders in this study included all patients with both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study.
- Spasm Control Response: Spasm Control Responders included all patients with cessation of spasms at any time during the study. Patients were evaluated for spasms through the treatment and follow-up periods. For the purpose of this analysis, Spasm Control Responders included all patients with cessation of spasms at any time during the treatment or follow-up periods identified by clinical assessment and/or parental reports that were recorded in the patient charts. Any patient noted to have cessation of spasm with who subsequently was observed to have spasms would be considered to have relapsed.

- Hypsarrhythmic EEG Pattern Response: Hypsarrhythmic EEG Pattern Responders included all patients with resolution of hypsarrhythmia as assessed by any post-treatment EEG at any time during the study. Serial long-term EEG and/or video monitoring studies (up to 24 hours) were used to determine the EEG response. If a patient had resolution of hypsarrhythmia on a post-treatment EEG but a later post –treatment EEG showed hypsarrhythmia, that patient would be considered relapsed.

The analysis of relapse was only performed in the Overall Responders in the mITT Population. A relapsed patient was defined as any patient in the mITT Population who, first, met the Overall Responder definition and then had 1 or both of the following conditions occur: 1) the patient demonstrated continued spasms or reduction of spasms following a noted cessation of spasms, or 2) the patient demonstrated any type of hypsarrhythmia on any EEG subsequent to an EEG that showed resolution of hypsarrhythmia.

For the ITT Population only, a sensitivity analysis was performed by applying the following "worst case scenario" definitions to patients with missing data in order to classify them as either Responders or Nonresponders for all 3 endpoints: the Spasm Control Response, the Hypsarrhythmia EEG Pattern Response, and then, by definition, the Overall Response, as follows:

- If a patient assigned to the Acthar low-dose group was not assessed for spasms cessation, then the patient was counted as a Spasm Control Responder.
- If a patient assigned to the Acthar low-dose group was not assessed for resolution of hypsarrhythmic EEG, then the patient was counted as a Hypsarrhythmic EEG Pattern Responder.
- If a patient assigned to the Acthar high-dose group was not assessed for spasms cessation, then the patient was counted as a Nonresponder for the Spasm Control Response.
- If a patient assigned to the Acthar high-dose group was not assessed for resolution of hypsarrhythmic EEG, then the patient was counted as a Nonresponder for Hypsarrhythmic EEG Pattern Response.

Results: The study enrolled 59 patients (30 high-dose, 29 low-dose). Nine patients (4 in the high-dose group, 5 in the low-dose group) did not complete the treatment protocol. Dr. Hrachovy was able to provide charts from 58 patients of the study patients: 50 who completed the study protocol and 8 of the 9 patients who prematurely withdrew from the study. The chart for the remaining patient could not be located.

Table 1.1 is a summary of the available dose record (exposure) data, efficacy data, and analysis populations by treatment group.

Table 1.1 Dose Record Data, Efficacy Data, and Analysis Populations by Treatment Group

	Acthar High Dose[a] n=30	Acthar Low Dose[b] n=29	Acthar All Patients N=59
Populations for Efficacy Analysis, n (%)			
ITT Population	30 (100.0)	29 (100.0)	59 (100.0)
mITT Population	24 (80.0)	27 (93.1)	51 (86.4)
Spasms Population	28 (93.3)	27 (93.1)	55 (93.2)
Completed Patients Population	26 (86.7)	24 (82.8)	50 (84.7)

a. Acthar High Dose: 150 U/m²/qd for 3 weeks, then 80 U/m²/qd for 2 weeks, then 80 U/m²/qod for 3 weeks, then 50 U/m² qod for 1 week, and then tapered to 0 U/qd over 3 weeks.

b. Acthar Low Dose: 20 U/qd for 2 weeks, then the dose was escalated or tapered based on response.

The median age of onset of spasms of all patients in the mITT Population was 6.62 months (range: 1.9 to 28.2 months). The median age of all patients was 6.7 months (range: 2 to 28 months) at start of treatment. The median lag time for all patients from date of diagnosis of IS to start of treatment was 0.1 month (range: 0 to 2 months). The median age of onset of spasms, the median age at start of treatment, and the median lag time to start of treatment was similar in the Acthar high-dose and the Acthar low-dose groups. More patients were male (31/51, 60.8%) than female (20/51, 39.2%); the Acthar low-dose group had a higher proportion of male patients (70.4%) than did the Acthar high-dose group (50.0%). The majority of patients had symptomatic etiology of IS (35/51, 68.6%). Consistent with a stratified design, the distribution of symptomatic and cryptogenic etiology of IS was similar in the Acthar high-dose (70.8% and 29.2%) and Acthar low-dose (66.7% and 33.3%) groups.

Table 1.2 is a summary overview of the primary, secondary, and confirmatory analyses.

Table 1.2 Summary Overview of Overall Response, Spasm Control Response, and Hypsarrhythmic EEG Pattern Response by Treatment Group (Each Efficacy Population)

Populations	Acthar Treatment[a,b]	N	Overall Response	Spasm Control Response	Hypsarrhythmic EEG Pattern Response
mITT Population	High Dose	24	*P*=0.2768	*P*=0.0329	*P*=0.2686
	Low Dose	27			
ITT Population[c]	High Dose	30	*P*=0.9443[d]	*P*=0.0691	*P*=0.5209[d]
	Low Dose	29			
Spasms Population	High Dose	28	*P*=0.6363	*P*=0.0126	*P*=0.6580
	Low Dose	27			
Completed Patients Population	High Dose	26	*P*=0.8225	*P*=0.0782[c]	*P*=0.8349
	Low Dose	24			

a. Acthar High Dose: 150 U/m²/qd for 3 weeks, then 80 U/m²/qd for 2 weeks, then 80 U/m²/qod for 3 weeks, then 50 U/m²/qod for 1 week, and then tapered to 0 U/qd over 3 weeks.

b. Acthar Low Dose: 20 U/qd for 2 weeks, then the dose was escalated or tapered based on response.

c. Sensitivity analysis, data imputed to favor Acthar Low Dose.

d. Mantel-Haenszel test was used to compare response rates between treatments, stratified on etiology. All contrasts showed numerically higher response rate for Acthar high-dose compared to Acthar low-dose except as noted.

Reviewer Note:
The records from this study do not indicate how many of the "low dose" arm patients were increased from 20 U QD to 30 U QD during the treatment period. The "High Dose" arm was given 150 U/m2/day QD which for most patients would be about 40 U QD.

The Questcor analyses of the efficacy data of CSR 222017-05 was as follows:

- In the mITT Population (the primary efficacy population), the Overall Response was similar in the Acthar high-dose (15/24, 62.5%) and the Acthar low-dose (13/27, 48.1%) groups, P=0.2768. However, the Spasm Control Response to treatment did demonstrate statistical significance: this response was greater in the Acthar high-dose group (19/24, 79.2%) than in the Acthar low-dose group (14/27, 51.9%), P=0.0329. The Hypsarrhythmic EEG Pattern Response was similar between the 2 treatment groups: Acthar high-dose (16/24, 66.7%) and the Acthar low-dose (14/27, 51.9%), P=0.2686.

- In the Spasms Population, the Spasm Control Response endpoint demonstrated statistical significance in that there were higher rates of response in the Acthar high-dose group (23/28, 82.1%) compared to the Acthar low-dose group (14/27, 51.9%), P=0.0126.

- A trend in the Spasm Control Response favoring the Acthar high-dose group was observed in both the ITT and Completed Patients Populations. The ITT sensitivity analysis, which used data imputation biased in favor of the Acthar low-dose group, showed a trend towards higher Spasm Control Response rates in the Acthar high-dose group (23/30, 76.7%) compared to the Acthar low-dose group (16/29, 55.2%), P=0.0691. In the Completed Patients Population, the treatment comparison was a Spasm Control Response rates in the Acthar high-dose group (21/26, 80.8%%) compared to the Acthar low-dose group (4/24, 58.3%),P=0.0782.

- In the mITT and Spasms Populations, the Spasm Control Response rates were higher for patients with cryptogenic IS etiology compared to symptomatic IS etiology in either dose group: Acthar high-dose (7/7, 100% compared to 12/17, 70.6%, respectively) versus Acthar low-dose group (6/9, 66.7% compared to 8/18, 44.4%, respectively).

- An exploratory analysis of relapse suggested that approximately 20% (3/15) of patients in the Acthar high-dose group and 15% (2/13) of patients in the Acthar low-dose group relapsed after treatment.

Questcor Conclusions for CSR 222017-05 efficacy: In the primary, mITT Population, the analysis of the Spasm Control Response by IS etiology showed a statistically significant difference between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose (P=0.0329). This statistical difference in favor of the Acthar high-dose by IS etiology was also demonstrated in the Spasms Population (P=0.0126).

A trend in favor of the Acthar high-dose group was also demonstrated in the ITT sensitivity analysis (P=0.0691) and in the Completed Patients Population (P=0.0782). In all cases, the Spasm Control Response rates appeared higher in patients with cryptogenic etiology compared to those with a symptomatic etiology in each dose group; however, the study was not designed nor was the study powered to make statistical conclusions about these observed differences based on IS etiology.

The analysis of Overall Response (spasms cessation and resolution of the hypsarrhythmic pattern on EEG) showed no statistically significant differences between the 2 treatment groups in any of the 4 defined populations. In addition, the analysis of the secondary endpoint of the remission of the Hypsarrhythmic EEG Pattern Response did not show any statistically significance differences between the 2 treatment groups in

any of the defined study populations. As previously stated, this study was underpowered in its ability to demonstrate differences between the 2 treatment groups.

In addition, both the Overall Response endpoint and the Hypsarrhythmic EEG Pattern Response were dependent on the EEG results. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150 U/m2/QD had been administered. In addition, there were patients in this study without any evidence of EEG testing after the initiation of Acthar treatment. Of note is that, in this study, Acthar was administered as a once-daily dose of 150 U/m2. Although this daily dose was equivalent to the total daily dose in CSR 222017-01, the Acthar in the CSR 222017-01 was administered as 2 divided daily doses (i.e., 75 U/m2 per dose). This difference in the dosing regimens results in a single ACTH plasma peak concentration in CSR 222017-05 compared to 2 ACTH plasma peak concentrations from the twice-daily dosing in CSR 222017-01.

The Sponsor concludes that the data from CSR 222017-05 at least support the efficacy of Acthar high-dose monotherapy with respect to one of the secondary endpoints (the Spasm Control Response) even when the daily dose was administered once a day rather than as a divided dose administered twice a day as in CSR 222017-01.

Reviewer Note:
As discussed previously in this review, the endpoint of clinical interest is the combined endpoint (Overall Response) of both spasm cessation and disappearance of hypsarrhythmia (the endpoint used in the pivotal study). There is no statistical significant difference between the two arms for this combined endpoint.

Why was there a lower response rate for the high dose arm in this supportive study compared to the pivotal study? There may have been differences in the patient population although the inclusion/exclusion criteria are similar. The most likely explanation seems to be that the pivotal study used a BID dosage for the high dose Acthar Gel which would be expected to give more sustained ACTH levels and a greater cortisol response

Assuming that the BID dosage accounts for the higher response rate for the high dose (150 U/m2/day) seen in the pivotal study (CSR 222017-01) in comparison to the supportive study (CSR 222017-05) and also assuming that the CSR 222017-05 secondary endpoint of spasm control response indicates greater efficacy from

the high dose arm compared to that of the low dose arm, the use of the high dose dosage given BID (as in the pivotal study) can be considered to be supported over the use of a lower dose or a QD dose. However, the data is not as definitive as it would have been in a prospective contemporaneous dose response study of several doses in a single randomized population of infants with IS.

Additional Data Analysis to Assess Acthar Efficacy: CSR 222017-04 (Hrachovy, 1983)

Questcor was also able to obtain the primary study data from a second clinical trial by Dr. Hrachovy and colleagues entitled, "Double-blind Study of ACTH versus Prednisone Therapy in Infantile Spasms." This study was a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day administered as a single daily (20 to 30 U/QD) IM dose (Acthar low-dose) to prednisone at a dose of 2 mg/kg/day PO in patients with IS (CSR 222017-04).

Eligibility Criteria: Patients enrolled in the study were diagnosed with IS (clinical spasms with hypsarrhythmic EEG patterns). All study patients were under the age of 4 years, had onset of spasms prior to age 12 months, and had spasms ongoing at the time of entry into the study. An infant previously treated with any steroid or ACTH or Acthar treatment was not eligible for the study. Informed consent was obtained from each patient's parent or guardian.

Evaluations: Before the initiation of treatment, patients were monitored for 24 to 48 hours to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored at 2 weeks and at 6 weeks after discontinuation of therapy. Patients were evaluated throughout the study for safety.

Treatment Protocol: Patients were randomly assigned to receive Acthar 20 U/QD IM and a prednisone placebo PO or prednisone 2 mg/kg/day PO and an Acthar placebo IM, for 2 weeks. Acthar and matching placebo were administered as a single dose/day. Prednisone and matching placebo were administered as 2 mg/kg/day.

If the patient responded to therapy within the first 2 weeks, the dosage of the drug was tapered to zero over a 1- to 2-week period. Then, the patient was monitored at 2 weeks and 6 weeks after discontinuation of therapy to substantiate a continued response. If a patient did not respond after the first 2 weeks, therapy was either changed to the other study drug (Acthar 30 U/QD or prednisone 2 mg/kg/day) or the originally assigned treatment was continued; this treatment was continued for an additional 4 weeks, after which study drug was tapered to zero over a 2-week period. Nonresponders to the initial 2 weeks of therapy or to the additional 4 weeks of therapy as were then crossed over to the other drug after a 1-week washout period and the protocol was repeated.

Efficacy Measures: The primary response to therapy in this study was defined as total cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. Spasms and hypsarrhythmic EEG pattern were assessed by serial 24-hour video and EEG monitoring.

Reviewers of the serial long-term EEG and video monitoring studies were unaware of patients' treatment group assignment. Secondary endpoints included in the analysis included EEG changes in nonresponders and changes in mental and developmental status.

Results: Twenty-four patients were enrolled in the study; 12 patients were randomly assigned to Acthar low-dose and prednisone placebo, and 12 patients were randomly assigned to prednisone and an Acthar placebo. A total of 19 patients (19/24, 79.2%) had symptomatic etiology of IS and 5 patients (5/24, 20.8%) had cryptogenic etiology of IS.

Questcor's analysis of the efficacy data demonstrated that the overall response rates in the initial treatment phase were 5/12 (41.7%) for Acthar low-dose and 4/12 (33.3%) for prednisone. The 95% 2-sided confidence intervals for the initial phase overall response were (15.2%, 72.3%) and (9.9%, 65.1%), respectively. Overall response rates were greater than the historical comparator rate of 5% for spontaneous remission through 3 months and 11% through 6 months (Hrachovy 1991) and were better than the placebo rate of 5% reported in a placebo-controlled, randomized, controlled trial of vigabatrin comparing the response rate (complete elimination of spasms and hypsarrhythmia) (Appleton 1999).

The overall response rates reported in this study, suggest that both therapies have some efficacy in the treatment of this disorder.

Conclusions: The overall response seen in these analyses to both Acthar low-dose and prednisone was similar between the 2 treatments. The response rates were higher than the reported spontaneous remission rates for this disease. These data indicated that both therapies provide some degree of efficacy for the treatment of patients with IS.

Reviewer Note:

There was no statistical difference between the two arms of the study. Although the comparison to the historical placebo spontaneous remission rate and to the placebo arm of the Appleton vigabatrin study (which had a different primary outcome) is interesting and somewhat reassuring, it is not conclusive. Therefore, the Sponsor is correct in considering this study as "additional data" rather than a pivotal or supportive study.

Safety Studies

See section 7.1.1 of this review for a discussion of the studies used for safety analysis.

6 Review of Efficacy

Because only one study was presented as pivotal, only one study as supportive, and only one study as additional evidence of efficacy, the three studies' results are presented individually in section 5.3 of this review. Additional discussion is available in the statistical review by Dr. Zhang.

6.1.7 Subpopulations

The small number of patients did not allow for a meaningful comparison of the response of patients with cryptogenic vs. symptomatic infantile spasms.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose response study was performed.

The "additional evidence" efficacy study, CSR 222017-04, studied Acthar low-dose 20 U/day (the same daily dose of Acthar Gel studied in CSR 222017-05) compared to the prednisone 2 mg/kg/day (the same daily dose of prednisone studied in CSR 222017-01). The data from CSR 222017-04 revealed no difference in the overall response between the patients randomized to Acthar low-dose compared to the patients randomized to prednisone. Of interest in this CSR 222017-04 study is that the response rate for the Acthar low-dose group of 5/12 (41.7%) was approximately the same response rate as was reported for the Acthar low-dose patients in the CSR 222017-05 mITT Population of 13/27 (48.1%). Similarly, the overall response for the prednisone patients in CSR 222017-04 of 4/12 (33.3%) is approximately the same response rate as was reported for the prednisone patients in CSR 222017-01 of 4/14 (28.6%). The concordance of the response rates of the two arms of CSR 222017-04 to the results seen with similar treatment arms in the two other studies, CSR 222017-01 and CSR 222017-05, provides some confirmation of the conclusions reached in the pivotal (CSR 222017-01) and supportive (CSR 222017-05) efficacy studies.

However, the data is not as definitive as it would have been in a prospective contemporaneous dose response study of several doses in a single randomized population of infants with IS.

6.1.9 Discussion of Persistence of Efficacy (Relapse) and/or Tolerance Effects

Given the relatively short-term treatment of 4 weeks (2 weeks of high dose with a two week taper) proposed in this NDA, it is important to consider what the relapse rate is after treatment is stopped. Unfortunately,the relapse data is very limited.

CSR 222017-01 (Baram 1996)

The publication and the clinical study report with protocol from the pivotal study CSR 222017-01 (Baram 1996) do not indicate how relapses were determined. The Sponsor was asked about method of recurrence detection on March 19, 2010 and replied that this could not be determined. For the purpose of my review, it is assumed that detection of a recurrence of spasms was based on caretakers notifying the investigators who may or may not have verified the recurrence with a video-EEG study. The fact that recurrence of spasms would be an "all-or-none" phenomenon suggests that the caretakers would be reasonably likely to detect a recurrence of spasms which would recur in clusters rather than subtle isolated spasms. Table 2 of the Baram publication shows that two of the 13 patients who responded to Acthar gel relapsed (a symptomatic female infant treated at 3 months of age and followed-up for 2 months; a symptomatic male infant treated at 6 months of age and followed-up for 17 months). This suggests a relapse rate of at least 2/13 (15%) but there is no indication as to how many months after treatment the recurrence was observed. Of the remaining 11 infants who responded to Acthar gel, 3 had no reported recurrence but were only followed for 1 month after treatment and 8 had no reported recurrence after being followed for 6 months or more (mean 17 months, range 6-37 months). Thus, it is possible that the recurrence rate was higher if one assumes that one or more of the infants with short follow-up times had a recurrence occurring after the time of follow-up with the investigators.

CSR 222017-05 (Hrachovy 1994)

The supportive efficacy study CSR 222017-05 (Hrachovy 1994) relied on caregiver report to detect relapse after the treatment period. If the caregiver reported relapse, this was verified with video-EEG monitoring. In the completed patient population, 13/26 high dose patients responded and 14/24 low dose patients responded. The relapse rate for the high dose arm responders was 2/13 patients (15%). In the published article, the relapse rate for the low dose arm responders was 3/14 patients (21%). There was no statistical difference between these relapse rates. Questcor re-analyzed the data using the response data for the mITT population and found similar relapse rates: 3/15 (20%) of responders in the high dose arm relapsed and 2/13 (15%) of the responders in the low dose arm relapsed.

Reviewer Note:

Although very limited, the relapse rate data suggests a relapse rate in the range of 15 to 30%. This is similar to the relapse rate range observed in studies of oral vigabatrin presented at the FDA PCNS Advisory Committee of January 8, 2009.

7 Review of Safety

Safety Summary

Reviewer Note: The Sponsor notified the Agency in a teleconference on March 22 that it intended to revise the "treatment groups" (dose categories based on the maximal daily dose of Acthar Gel received) used to integrate the safety data across safety studies in their NDA submission (see 7.1.3 and 7.2.1 of this review). This will mean that the safety summary tables concerning the 319 patients (see section 7.1.1 of this review) in the Sponsor's pending briefing document for the Advisory Committee will probably differ slightly from the summary tables presented in their NDA submission and reviewed in this review.

7.1 Methods

This section reviews the safety data presented by the Sponsor in the integrated summary of safety, in the clinical study reports from the individual studies cited in section 7.1.1 below, and from the published articles from the three studies discussed in the efficacy section of this review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Questcor could not obtain safety data from the pivotal study (CSR222-017-01, Baram) although these patients are presumed to be among the patients evaluated in the retrospective chart review by Partikian and Mitchell discussed below as CSR 222017-02.

Questcor obtained source safety data from the following 4 studies:

A study conducted by Partikian and Mitchell (Partikian 2007). Questcor's analyses of these safety data are presented in this Complete Response as CSR 222017-02. This study presumably contained the safety data for the patients treated in the randomized controlled trial conducted by Baram and reported in this submission as CSR 222017-01.

Questcor also conducted its own protocol to obtain safety data from patients treated at 4 clinical sites in the United States. These data are presented in this Complete Response as CSR QSC007-ACT-002.

Questcor obtained source data from the 2 of the RCTs conducted and published by Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983); Questcor's independent analyses of these data are presented in this Complete Response as CSR 222017-05 and CSR 222017-04, respectively.

These four studies are shown in the table below.

Study	Description	Number of Acthar Gel-treated patients contributed to Integrated Safety Tables
CSR 222017-02	Partikian and Mitchell retrospective chart review	84
CSR QSC007-ACT-002	Questcor retrospective chart review at 4 sites	178
CSR 222017-05	Hrachovy 1994 Study of Acthar Gel High vs Low Dose (charts reviewed retrospectively for safety data)	57
CSR 222017-04	Hrachovy 1983 study of ACTH vs Prednisone (patients on Acthar gel not identifiable in retrospective chart review)	None
Total patients in Integrated Safety Tables		**319**

The division of the 319 patients into three dosage categories (Questcor Recommended Dose, Other High Dose, and Low Dose) is discussed in section 7.2.1 of this review.

These four studies are summarized in the following paragraphs.

CSR 222017-02

Clinical study report CSR 222017-02, entitled, "Retrospective Analysis of Adverse Events Associated with Treatment of Infantile Spasms with Acthar Gel," was a retrospective chart review. The primary objective of this study was to analyze retrospective data provided by Drs. Partikian and Mitchell to assess the safety and tolerability of Acthar administered using a standard treatment schedule consisting of a

treatment phase followed by a taper phase. The secondary objective was to report the safety data from patients reported in the pivotal efficacy study that compared Acthar to prednisone in patients with IS (CSR 222017-01); safety data from these patients were likely contained within the data obtained from Drs. Partikian and Mitchell for this analysis based on the dates of treatment. Questcor obtained the safety data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in CSR 222017-02.

Study Design: Drs. Partikian and Mitchell reviewed the charts of all patients with IS (International Classification of Diseases code 345.6) admitted to Childrens Hospital of Los Angeles (CHLA) between January 1990 and August 2006 (Partikian 2007). In addition, they identified outpatients from Neurology Division records of patients with IS whose treatment was initiated without hospital admission. Data from the chart review were collected on data collection forms developed by the Investigators. Drs. Partikian and Mitchell provided these completed forms to Questcor; Questcor then performed its own independent analysis of these data.

Patients were included in the study based on the diagnosis of IS, with spasms confirmed by either clinical observation or on video-EEG, with EEG evidence of classical or modified hypsarrhythmia or multifocal independent spike discharges. Patients with an atypical EEG pattern were included if an attending pediatric neurologist intended to treat the child as having IS based on clinical criteria of spasms with psychomotor regression.

Demographic characteristics and baseline variables included sex, age at onset of spasms and onset of treatment, lag time from onset of spasms to initiation of treatment, etiology, IS history, developmental status, previous treatment with antiepileptic drugs (AEDs), and pre-existing medical conditions. Treatment variables included initial treatment type, drug dosage, and schedule of administration.

Treatment Protocol: Not all patients received Acthar Gel. Treatment choice was made by the attending child neurologist for the individual patient and not by randomization. When Acthar Gel treatment was chosen, Acthar treatment was administered by IM injection according to a standard protocol. The treatment schedule started with 150 U/m2/day divided into 2 daily doses for the first 1 to 2 weeks, and then tapered beginning with 75 U/m2/day for 1 week, then tapered rapidly to an alternate-day schedule for the next 3 to 4 weeks, which was followed by taper-off treatment. Treatment intervals could not be confirmed from the data provided.

Safety Measures: Assessments of safety and tolerability were collected from patient charts at baseline and at 3 follow-up intervals. The first follow-up interval included all visits that occurred 1 to 3 weeks after initiation of treatment. The second follow-up interval included all visits that occurred 4 to 8 weeks after the start of therapy. The third

follow-up interval included visits that occurred 3 or more months after treatment initiation. Safety measures included AEs (parent-reported, major, and serious AEs [SAEs], changes in weight and blood pressure [BP]), changes in medication, and development of new seizure during the treatment period.

Results: The Questcor database had data from 130 patients (each receiving either Acthar Gel or an alternative therapy) from the original published study (Partikian 2007), consisting of patients treated at CHLA between January 1990 and August 2006 for IS, and also data from 29 additional patients, consisting of patients with IS treated at CHLA since the end of the original study through April 2008. The 130 patients from the original published study included **20** patients who received Acthar as initial treatment for IS in the era of the Baram 1996 study (Era 1) and **45** patients who received Acthar as initial treatment for IS after the era of the Baram 1996 study (Era 2). Of the 29 additional patients, **19** received Acthar as initial treatment for IS (Era 3).

Therefore, a total of 84 patients (20 + 45 + 19) received Acthar as initial treatment for IS (Overall: Eras 1, 2, and 3, combined). The analysis of safety for patients who received Acthar as initial treatment for IS in this retrospective data review is as follows:

• Parent-reported AEs consisted largely of irritability, excessive appetite, infections, and sleep difficulties. These tended to be reported during the first follow-up interval, when the patients were on the highest dose of drug, and decreased over time as the drug was tapered and discontinued.

• More than 33% (28/84) had at least 1 potentially significant systolic BP (SBP) measurement during the first follow-up interval compared with only 17.9% (15/84) at baseline. The number of patients with potentially significant SBP measurements decreased to 21.4 % and 3.6% during the second (18/84) and third (3/84) follow-up intervals, respectively. The results for diastolic BP (DBP) were similar, where 23.8% (20/84) had potentially significant measurements during the first follow-up interval compared with 14.3% (12/84) of patients at baseline. The number of patients noted to have potentially significant DBP measurements decreased to 10.7% and 4.8% during the second (9/84) and third (4/84) follow-up intervals, respectively.

• The most common SAEs included nervous system disorders, infections, and hospitalizations. The nervous system disorders were all seizure-related, but it was not possible to separate new seizures from exacerbations of the IS or progression of IS to other seizure disorders.

• Common laboratory abnormalities reported included white blood cell elevation, low serum potassium, elevated liver function tests, and low hemoglobin.

Mean change from baseline for weight averaged 11.6%, 17.8%, and 25.7% over the first, second, and third follow-up intervals, respectively. The increases in weight over time may have been due to both background growth in infants as well as to Acthar-induced weight gain.

• Safety results for patients who received Acthar during Era 1, representing patients previously evaluated for efficacy by Questcor (CSR 222017-01), were consistent with the safety findings for the patients who received Acthar in Era 2 and Era 3.

• There were no SAEs reported for patients who received prednisone in Era 1 of this study. This may be related to the fact that these patients appeared to have a shorter duration of therapy when compared to Acthar, possibly due to lack of efficacy of the prednisone treatment for IS.

Sponsor's Conclusions: The AEs reported in this study in patients treated with Acthar are well known to occur with this therapy. None of the findings from this retrospective chart review were unexpected. The AEs reported are readily recognized and managed by routine clinical care and medical interventions. In particular, blood pressure elevations that may occur with Acthar may be managed, if medically necessary, with antihypertensive drug therapy.

CSR QSC007-ACT-002

Clinical study report CSR QSC007-ACT-002, entitled, "Determination of the Adverse Effect Profile for Patients with Infantile Spasms Treated with H.P. Acthar Gel (ACTH): A Retrospective Review," was a retrospective chart review study to determine the AE profile of patients with IS treated with Acthar. Patients were included in the study based on the diagnosis of IS and age at first treatment with Acthar.

The primary objective of this study was to assess the AE profile in patients with IS treated with Acthar high-dose (approximately 150 U/m2/day [range from 125 to 175 U/m2/day]) given in 2 divided doses administered to patients from January 2000 to 01 May 2008 at 4 participating clinical centers.

Study Design: Data review and capture was planned for the period January 2000 to 01 May 2008. Potential cases were identified by querying the hospital, pharmacy, and/or clinical records for patients from the years 2000 through 2008. The data were extracted from clinic and/or hospital charts including the treating doctors' notes, EEG reports, magnetic resonance imaging reports, and other clinical information.

For the data analysis, patients were categorized into 1 of 3 treatment groups based on the maximum daily dose of Acthar administered as shown below:
• Questcor Recommended Dose: 150 U/m2/day (Dose range within the range ≥ 135 and ≤ 160 U/m2/day), divided, bid
• Other High Dose: Dose ≥ 80 U/m2/day but outside the Recommended Dose (included patients with a maximum dose ≥ 80 U/m2/day but outside the Recommended Dose range and patients with a maximum dose within the Recommended Dose range that was not administered divided bid)
• Low Dose: Dose < 80 U/m2/day

Treatment Protocol: Acthar treatment was administered by IM injection according to clinical practice at each study site.

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR QSC007-ACT-002).

Safety Measures: For assessment of AEs, data were collected from patient charts at baseline, at subsequent visits for evaluation of Acthar treatment, and at a final visit. The final visit was defined as any clinic visit that occurred at least 2 weeks following the final dose of Acthar or the last recorded visit at or near 2 weeks.

Results: One hundred and seventy-eight (178) patients were included in the analysis data set. Analysis of data from this retrospective study of patients who received Acthar as treatment for IS demonstrated the following:

- Over half of all patients (59.0%, 105/178) experienced 1 or more AEs during the study. The proportions of patients with 1 or more AE were similar in the Other High Dose and Recommended Dose groups (67/105, 63.8% and 31/50, 62.0%, respectively). The Low Dose group had the smallest proportion of patients with 1 or more AEs (7/23, 30.4%).
- The most common AEs in all groups combined were: irritability (16.3%), Cushingoid appearance (9.6%), hypertension (9.6%), and increased appetite (6.2%). The most common AEs (occurring in >5% of all patients) in the Recommended Dose group were hypertension (18.0%), irritability (12.0%), and left ventricular hypertrophy (LVH) (8.0%). In the Other High Dose group, the most common AEs were irritability (19.0%), Cushingoid appearance (13.3%), increased appetite (10.5%) and hypertension (6.7%). The most common AEs in the Low Dose group were irritability (13.0%), Cushingoid appearance (4.3%), and hypertension (4.3%).
- There were 20 patients overall who experienced 1 or more SAEs during the study, most of which were judged to be related (possibly, likely) and were consistent with the known pharmacology of Acthar. Most patients required no treatment or were adequately treated with medication for the resolution of their SAE.
- One death, due to aspiration pneumonia, was reported in the Other High Dose group and considered to be possibly due to Acthar treatment.
- The most common parent-reported AEs in all patients were irritability, upper gastrointestinal irritability or gastroesophageal reflux disease, infections, drowsiness, sleep difficulties, reduced appetite, respiratory difficulties, excessive appetite, fever, and increased secretions/drooling.
- During the first follow-up interval, 14.0% (25/178) of patients had a planned downward titration of Acthar and 3.9% (7/178) of patients had Acthar decreased prematurely due to an AE. In the second follow-up interval, 73.6% (131/178) of

patients had a planned downward titration of Acthar and 0.6% (1/178) of patients had Acthar decreased prematurely due to an AE.

- There were multiple patients with abnormal laboratory values throughout the study; very few resulted in an action being taken by the investigator.
- There were reversible increases in SBP, DBP, and potentially significant BPs during Acthar treatment, which returned to baseline following discontinuation of treatment. These tended to be more frequent in the Recommended Dose group and Other High Dose group compared to the Low Dose group, but the differences between treatment groups were not significant.

Sponsor's Conclusions: Analysis of data from this retrospective study of patients who received Acthar as treatment for IS demonstrated the following:

- The AEs reported in this study are well known to occur with Acthar administration in patients with IS. None of the findings from this retrospective chart review were unexpected.
- The AEs reported were readily recognized and managed by routine clinical care and medical interventions. In particular, blood pressure elevations that occurred with Acthar were readily managed, if medically necessary, with antihypertensive drug therapy.

CSR 222017-05

"High-dose, Long-duration versus Low-dose, Short-duration Corticotropin Therapy for Infantile Spasms" was a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen to Acthar low-dose regimen in patients with IS.

The Acthar high-dose regimen consisted of Acthar given at a dose of 150 U/m2/day as a single IM dose for 3 weeks followed by a 9-week taper; the Acthar low-dose regimen consisted of Acthar 20 U/day as a single IM dose for 2 weeks followed by a 2-week taper in responders or a dose escalation to 30 U/day in nonresponders. The principal investigator, Dr. Hrachovy and his colleagues had previously published the study results from their analyses of the data (Hrachovy 1994). Questcor obtained the source data from the investigators, and with the investigators' permission, Questcor performed an independent analysis for submission in this sNDA; these analyses are presented in the clinical study report CSR 222017-05.

Study Design: Patients enrolled in the study were diagnosed with IS defined by both the presence of clinical spasms and a hypsarrhythmic EEG pattern. All study participants were under the age of 4 years, had onset of spasms prior to the age of 12 months, and continued to have spasms at the time of entry into the study. Patients who had previously received ACTH or Acthar or corticosteroid therapy for their spasms were not

eligible for the study. Informed consent was obtained from each patient's parent or guardian.

Prior to the initiation of treatment, patients were monitored using a video-EEG for up to 24 hours in order to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored with video-EEGs 2 to 3 times during the treatment period; the treatment period was 12 weeks for the high-dose and 6 weeks for low-dose. As per the study protocol, the 2 dosing groups had different schedules as to when the post-Acthar EEGs were to be performed. The patients randomly assigned to the Acthar low-dose group were scheduled to have their first post-Acthar EEG performed 2 weeks after the start of treatment, whereas patients in the Acthar high-dose group did not have their first post-Acthar EEG performed until after the Acthar was tapered to zero, a full 12 weeks after the initiation of therapy and 9 weeks after the maintenance dose of 150 U/m2/qd had been administered. Patients were evaluated throughout the study for spasm cessation and safety.

Treatment Protocol: Eligible patients were first stratified as having either cryptogenic or symptomatic IS and then randomized to receive treatment with either high-dose Acthar (150 U/m2/day administered as a single daily dose IM for 3 weeks, followed by 80 U/m2/day IM for 2 weeks, then 80 U/m2/qod IM for 3 weeks, then 50 U/m2/qod IM for 1 week, and then Acthar was tapered to zero over 3 weeks) or Acthar low-dose (a single daily dose of 20 U/day IM for 2 weeks). Nonresponders to the high-dose Acthar regimen were treated with prednisone 2 mg/kg/day orally (PO) for 4 to 6 weeks, and then followed in a routine clinical manner. Nonresponders to low-dose Acthar had their Acthar increased to 30 U/day for an additional 4 weeks followed by a taper to zero over a 2-week period.

There were 57 patients in the Safety Population (patients who received at least one dose of Acthar Gel).

Data Methods: Procedures used to collect, to analyze, and to ensure the integrity of study data are provided in the final study report (see CSR 222017-05).

Safety Measures: Patients were monitored for safety throughout the study. Adverse events were recorded to the patient charts as were the results of clinical laboratory evaluations (complete blood count [CBC], blood glucose, electrolytes, urinalysis), vital signs (BP, height, weight, pulse and respiratory rates), concomitant medications, physical examination findings, chest x-rays, and other imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]), as required.

Results:

- The majority of patients (51/57, 89.5%) had 1 or more AEs during the study. The rate of AEs in the Acthar high-dose group (26/28, 92.9%) was similar to that in the Acthar low-dose group (25/29, 86.2%).

- The most frequently reported (≥ 10% of patients) AEs in Acthar-treated patients (high-dose and low-dose) were candidiasis (10/28, 35.7% and 11/29, 37.9%), Cushingoid appearance (8/28, 28.6% and 6/29, 20.7%), otitis media (7/28, 25.0% and 6/29, 20.7%), irritability (4/28, 14.3% and 5/29, 17.2%), pyrexia (5/17.9% and 4/29, 13.8%), acne (6/21.4% and 3/29, 10.3%), diarrhea (6/28, 21.4% and 2/29, 6.9%), blood pressure increase (5/28, 17.9% and 2/29, 6.9%), and vomiting (3/28, 10.7% and 3/29, 10.3%).
- The most frequently reported (≥ 10% of patients) parent-reported AEs in Acthar-treated patients (high-dose and low-dose) at any time during the entire follow-up period were drowsiness (5/28, 17.9% and 3/29, 10.3%), irritability (23/28, 82.1% and 20/29, 69.0%), sleep difficulties (13/28, 46.4% and 10/29, 34.5%), excessive appetite (14/28, 50.0% and 7/29, 24.1%), reduced appetite (12/28, 42.9% and 9/29, 31.0%), infections (11/28, 39.3% and 12/29, 41.4%), fever (8/28, 28.6% and 9/29, 31.0%), and respiratory difficulties (7/28, 25.0% and 3/29, 10.3%).
- The most frequently reported (≥ 10% of patients) physical examination findings in Acthar-treated patients (high-dose and low-dose) at any time during the entire follow-up period were facial rash (15/28, 53.6% and 10/29, 34.5%), thrush (oral) (12/28, 42.9% and 10/29, 34.5%), skin (other rashes, hyperpigmentation) (17/28, 60.7% and 7/29, 24.1%), Cushingoid features (12/28, 42.9% and 10/29, 34.5%), muscular abnormality (7/28, 25.0% and 0/29, 0.0%), and dysmorphic feature (5/28, 17.9% and 2/29, 6.9%).
- There was 1 death in the study. Patient 90-004 was a 3.3 month-old male infant with a history of IS, microcephaly, and severe developmental delay at the start of treatment who was repeatedly hospitalized with severe respiratory symptoms, developed pulmonary edema, respiratory failure, and died of cardiac arrest at (b) (6) months of age. The patient was treated with Acthar doses of 20 to 40 U/qd over several weeks.
- Nine (9) patients (4 Acthar high-dose, 5 Acthar low-dose) had 1 or more SAEs during the study. Serious AEs in the Acthar high-dose group were dehydration, bronchopneumonia, increased blood pressure, skin discoloration, and decreased appetite. Serious AEs in the Acthar low-dose group were bronchiolitis, acute respiratory distress syndrome, pneumonia, pulmonary edema, respiratory failure, and cardiac arrest, status epilepticus, otitis media, dyspnea, and cellulitis.
- There was no difference between the 2 dose groups in the number of patients who discontinued the study early due to AEs. Four (4) patients (1 Acthar high-dose, 3 Acthar low-dose) had 1 or more AEs leading to discontinuation during the study. The AEs were increased blood pressure and skin discoloration in the patients in the Acthar high dose group, and pyrexia, increased blood pressure, and otitis media in the patients in the Acthar low-dose group.

Sponsor's Conclusions: The AEs in this study reported in patients assigned to the Acthar high-dose regimen are well known and are readily managed by routine clinical care and routine medical intervention. Acthar high-dose has an acceptable benefit-risk

profile for the treatment of patients with IS, particularly given the catastrophic nature of this disorder if left untreated.

CSR 222017-04

Questcor was also able to obtain the primary study data from a second clinical trial by Dr. Hrachovy and colleagues entitled, “Double-blind Study of ACTH [Acthar] versus Prednisone Therapy in Infantile Spasms.” This study was a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day given IM as a single daily dose (Acthar low-dose) to oral prednisone 2 mg/kg/day in patients with IS.

Reviewer Note: As discussed below under “Results” of this study, the safety data from these CSR 222017-04 patients could not be included in the integrated safety tables since the treatment arm to which each patient had been assigned could not be determined during the retrospective chart review for safety data.

Eligibility Criteria: Patients enrolled in the study were diagnosed with IS (clinical spasms with hypsarrhythmic EEG patterns). All study patients were under the age of 4 years, had onset of spasms prior to age l2 months, and had spasms ongoing at the time of entry into the study. An infant previously treated with any steroid, Acthar or ACTH treatment was not eligible for the study. Informed consent was obtained from each patient’s parent or guardian.

Evaluations: Before the initiation of treatment, patients were monitored for 24 to 48 hours to confirm the presence of IS and to establish a baseline seizure frequency. Patients were monitored at 2 weeks and at 6 weeks after discontinuation of therapy. Patients were evaluated throughout the study for safety.

Treatment Protocol: Patients were randomly assigned to receive Acthar low-dose 20 U/day IM and a prednisone placebo PO or prednisone 2 mg/kg/day PO and an Acthar placebo IM, for 2 weeks. Acthar low-dose and matching placebo were administered as a single dose/day. Prednisone (2 mg/kg/day) and matching placebo were administered as a single dose/day. If the patient responded to therapy within the first 2 weeks, the dosage of the drug was tapered to zero over a 1- to 2-week period. Then, the patient was monitored at 2 weeks and 6 weeks after discontinuation of therapy to substantiate a continued response. If a patient did not respond after the first 2 weeks, therapy was either changed to the other study drug (Acthar 30 U/day or prednisone 2 mg/kg/day) or the originally assigned treatment was continued; this treatment was continued for an additional 4 weeks, after which study drug was tapered to zero over a 2 week period. Nonresponders to the initial 2 weeks of therapy or to the additional 4 weeks of therapy as were then crossed over to the other drug after a 1-week washout period and the protocol was repeated.

Safety Measures: Safety was evaluated throughout the study. The Questcor analysis, however, only included the safety measures that were reported in the study publication, specifically, the incidence of sustained high BP > 140/90 mmHg and cerebral shrinkage. **When the patient charts were obtained for a retrospective chart review for safety data (as had been done with CSR 222017-05), there was no method to determine into which treatment arm the patients had been assigned.**

Results: Twenty-four patients were enrolled in the study; 12 patients were randomly assigned to Acthar low-dose and prednisone placebo, and 12 patients were randomly assigned to prednisone and an Acthar placebo. A total of 19 patients (19/24, 79.2%) had symptomatic etiology of IS and 5 patients (5/24, 20.8%) had cryptogenic etiology of IS.

With respect to safety, limitations of the data available from the chart review did not permit confirmation of published results. Specifically, the data on adverse findings were not attributable to one arm of the study versus the other (low dose ACTH vs oral prednisone). Therefore, this data from CSR 222017-04 was not integrated into the integrated safety results of the three other studies [CSR 222017-02, the Questcor Retrospective Safety Study (CSR QSC007-ACT-002), and CSR 222017-05].

Questcor's analysis of the safety data demonstrated the following:

- Isolated instances of elevated BP >140/90 mmHg occurred during the study but no information was available to confirm that there were sustained elevations in BP.
- The numbers of patients with CT scans showing evidence of brain shrinkage were too few in number to draw any conclusions regarding the effect of treatment.

Sponsor's Conclusions: With respect to safety, limitations of the data available from the chart review did not permit confirmation of published results.

- Patients treated with Acthar or prednisone showed evidence of increased ventricular size or increased subarachnoid space, or both. The numbers of patients with CT scans showing evidence of brain shrinkage were too few in number to draw any conclusions regarding the effect of treatment.
- Hypertension developed with both Acthar and prednisone treatment. Isolated instances of elevated BP >140/90 mmHg occurred during the study but no information was available to confirm that there were sustained elevations in BP.

Reviewer's comment:

NDA submissions usually have blinded prospective safety data from pivotal trials collected during the study according to a prospective protocol. This quality of safety data is not available for this submission.

Supportive study CSR 222017-05 was a prospective efficacy study but the safety data was collected by an unblinded retrospective chart review of the participating patients according to a retrospective protocol for collection for safety data. A similar retrospective chart review was not possible for pivotal study CSR 222017-01 or for study CSR 222017-04 as discussed above.

Studies CSR 222017-02 and CSR QSC007-ACT-002 are retrospective chart reviews of larger numbers of patients the majority of which were not enrolled in a clinical study. They offer a larger, arguably more representative sample of the proposed treatment population.

7.1.2 Categorization of Adverse Events

Serious adverse events were those adverse events that required that the patient have an emergency room visit and/or hospitalization.
Significant adverse events were those occurring in $\geq$ 2% of the total patients (319 patients).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The study population in the analysis of safety integrated across clinical studies included patients from 3 of the 4 clinical studies from which safety data were available [CSR 222017-02, the Questcor Retrospective Safety Study (CSR QSC007-ACT-002), and CSR 222017-05].

Safety data from CSR 222017-04 were not included in the integrated safety summary because of the inability to clearly identify and link the AEs to the specific study treatments evaluated in this particular trial, i.e., Acthar low-dose or prednisone; consequently, these data are presented separately at the end of section 7.1.1 of this review.

Integration of safety data from the above-mentioned 3 studies was performed based on the maximum daily dose of Acthar received by patients at the start of treatment. Patients were categorized into treatment groups based on the maximum daily dose of Acthar received regardless of any prior treatment received before Acthar initiation. Dose categories corresponded with Acthar dose

in the proposed label for the treatment of IS (Questcor Recommended Dose) as well as with other dose categories commonly reported in the literature (Other High Dose and Low Dose) as follows:

- Questcor Recommended Dose: Acthar dose of 150 U/m2/day (dose range within the range ≥ 135 to ≤ 160 U/m2/day), divided, bid, administered for 2 weeks
- Other High Dose: Acthar dose ≥ 80 U/m2/day (included patients with a maximum dose ≥ 80 U/m2/day and patients within the Questcor Recommended Dose range where Acthar was not administered as a divided, twice-daily dose)
- Low Dose: Acthar dose <80 U/m2/day (this includes patients who received Acthar 20 U/day in CSR 222017-05)

The designation of the dosing categories, “Other High Dose” and “Low Dose,” was established by Questcor to define Acthar dosing schedules that were different from the Questcor proposed dosing schedule. These designations, “Other High Dose” and “Low Dose,” were based on an arbitrary daily dose of 80 U/m2/day. In addition, patients included in the “Other High Dose” category received a daily Acthar dose that may have been 150 U/m2/day, but the drug was administered as a single daily dose instead of as 2 divided doses, the Questcor recommended dosing schedule.

In all cases where the dose administered to the patient was presented as U/day, Questcor did calculations to present the dose as U/m2/day. These calculations were based upon the data provided in the patient charts. Questcor calculations revealed that patients who received the Questcor proposed dosing schedule of 150 U/m2/day revealed an actual dose range of 135 to 160 U/m2/day (likely due to practical issues around the withdrawal of the actual Acthar dose from the drug vial). Therefore, for this integrated safety summary, the Recommended Dose group of 150 U/m2/day dosing schedule included patients whose actual dose ranged from 135 to 160 U/m2/day administered IM in 2 divided doses.
All safety data presented in this section reflect data integrated from 3 of the 4 studies.

7.2 Adequacy of Safety Assessments

See discussion in section 3.1 of this review concerning safety data quality.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The number of patients from each study that contributed data to each treatment group is shown in the Sponsor's Table 1.1.

Table 1.1 Numbers of Patients from Clinical Safety Studies Contributing Data to Integrated Analysis

Study	Questcor Recommended Dose[a] n=134	Other High Dose[a] n=133	Low Dose[a] n=52	All Patients[a] N=319
CSR 222017-02	84	0	0	84
CSR QSC007-ACT-002	50	105	23	178
CSR 222017-05	0	28	29	57

a. Dose groups are defined in Section 1.4.5.

NOTE: Safety data from the Hrachovy Acthar versus prednisone study (CSR 222017-04) were not included in the integrated summary because of the inability to identify and link the AEs resulting from Acthar or prednisone therapies for the majority of patients.

Source: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

Demographics

Demographics and other baseline characteristics are summarized by treatment group in the sponsor's Table 1.2.
The mean (± standard deviation [SD]) age of all 319 patients at IS diagnosis was 7.7 months (± 5.04 months) and was similar across the 3 treatment groups. Consistent with the known epidemiology of IS, there was a slight preponderance of male patients (187/319, 58.6%).
The mean (± SD) weight of patients was 8.2 kg (± 1.92 kg) and mean (± SD) height of patients was 68.9 cm (± 7.78 cm). The mean (± SD) body surface area (BSA) was 0.397 m2 (± 0.0665 m2). In most patients, information concerning race was not available for analysis (135/319, 42.3%). In those patients with data, the majority were Caucasian (White) (122/319, 38.2%), or African-American (Black) (49/319, 15.4%).

As has been the case in all reported studies, the majority of patients had a symptomatic etiology of IS (189/319, 59.2%). There were, however, a substantial number of cryptogenic cases (122/319, 38.2%) in the study population, which allowed assessment of safety in this group as well.

Table 1.2 Overall Summary of Demographic and Baseline Characteristics by Treatment

Characteristic	Questcor Recommended Dose[a] (n=134)	Other High Dose[a] (n=133)	Low Dose[a] (n=52)	All Patients[a] (N=319)
Age at start of IS treatment (m)				
N[b]	133	126	46	305
Mean	8.2	8.5	9.0	8.4
SD	5.09	5.33	5.78	5.29
Median	7.0	7.5	7.1	7.2
Min, Max	0, 33	1, 36	2, 28	0, 36
Gender, n (%)				
Male	77 (57.5)	74 (55.6)	36 (69.2)	187 (58.6)
Female	57 (42.5)	59 (44.4)	15 (28.8)	131 (41.1)
Race, n (%)				
White	29 (21.6)	70 (52.6)	23 (44.2)	122 (38.2)
Black or African-American	13 (9.7)	27 (20.3)	9 (17.3)	49 (15.4)
Asian	2 (1.5)	4 (3.0)	1 (1.9)	7 (2.2)
Other	2 (1.5)	3 (2.3)	1 (1.9)	6 (1.9)
Unknown	88 (65.7)	29 (21.8)	18 (34.6)	135 (42.3)
Ethnicity, n (%)				
Hispanic or Latino	25 (18.7)	23 (17.3)	11 (21.2)	59 (18.5)
Non-Hispanic or Non-Latino	21 (15.7)	83 (62.4)	19 (36.5)	123 (38.6)
Unknown	88 (65.7)	27 (20.3)	22 (42.3)	137 (42.9)
Height, cm				
N[b]	130	110	42	282
Mean	69.0	68.4	69.8	68.9
SD	7.56	7.63	8.87	7.78
Median	68.3	68.7	69.8	68.7
Min, Max	52, 91	49, 97	55, 90	49, 97
Weight, kg				
N[b]	133	133	51	317
Mean	8.3	8.0	8.5	8.2
SD	1.85	1.83	2.29	1.92
Median	8.4	7.9	8.3	8.2
Min, Max	4, 13	5, 14	4, 14	4, 14

Characteristic	Questcor Recommended Dose[a] (n=134)	Other High Dose[a] (n=133)	Low Dose[a] (n=52)	All Patients[a] (N=319)
Body Surface Area, m^2				
N[b]	134	133	51	318
Mean	0.398	0.392	0.409	0.397
SD	0.0633	0.0640	0.0798	0.0665
Median	0.397	0.389	0.409	0.397
Min, Max	0.24, 0.57	0.25, 0.61	0.26, 0,60	0.24, 0.61
Etiology Category, n (%)				
Cryptogenic	44 (32.8)	57 (42.9)	21 (40.4)	122 (38.2)
Symptomatic	89 (66.4)	71 (53.4)	29 (55.8)	189 (59.2)
Unknown	1 (0.7)	5 (3.8)	2 (3.8)	8 (2.5)

a. Dose groups are defined in Section 1.4.5
b. The number of patients with data available are provided where data were missing for some patients.
Source: Section 1.12.3, Table 6.12.1: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.2.2 Explorations for Dose Response
The absence of a formal dose response study is discussed in section 6.1.8 of this review with respect to efficacy.

The integrated safety tables have been formulated with three dose categories discussed in section 7.2.1 of this review.

7.2.3 Special Animal and/or In Vitro Testing
Not applicable

7.2.4 Routine Clinical Testing
Included vital signs, physical and neurological assessment, clinical laboratory assessment as available from retrospective chart review.

7.2.5 Metabolic, Clearance, and Interaction Workup
Not applicable

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class
The Sponsor summarized selected Adverse effects expected from clinical experience with ACTH and steroid medications in Sponsor's Table 1.5 reproduced below.

Table 1.5 Overall Summary of Selected Adverse Events by Treatment Group

Selected Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Patients with at least 1 AE	**36 (26.9)**	**77 (57.9)**	**25 (48.1)**	**138 (43.3)**
Patients with No AEs	**98 (73.1)**	**56 (42.1)**	**27 (51.9)**	**181 (56.7)**
Infections	25 (18.7)	32 (24.1)	16 (30.8)	73 (22.9)
Irritability	8 (6.0)	26 (19.5)	8 (15.4)	42 (13.2)
Cushingoid	3 (2.2)	25 (18.8)	8 (15.4)	36 (11.3)
Hypertension	13 (9.7)	16 (12.0)	5 (9.6)	34 (10.7)
Increased appetite	0 (0.0)	12 (9.0)	1 (1.9)	13 (4.1)
Weight gain	1 (0.7)	7 (5.3)	0 (0.0)	8 (2.5)
Cardiac hypertrophy	4 (3.0)	1 (0.8)	0 (0.0)	5 (1.6)
Hyperglycemia	1 (0.7)	2 (1.5)	0 (0.0)	3 (0.9)
Hypokalemia	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.6)

a. Dose groups are defined in Section 1.4.5.
Source: Section 1.12.3, Table 6.12.5,: CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the publication (Baram, 1996) of the pivotal efficacy study (CSR 222017-01). Safety data on the patients from this study are presumed to be included in the retrospective safety study by Partikian (CSR 222017-02) which reported only one death. This infant had not been part of the data analysis since the infant did not meet the criteria of being treated for infantile spasms at the author's institution but was subsequently admitted to this institution while being treated with a prolonged (b) month course of Acthar Gel combined with (b) weeks of valproate therapy. This child died of pneumonia attributable to prolonged ACTH therapy.

One death was reported from CSR 222017-05. This infant had a history of microcephaly and severe developmental delay and was randomized at age 3.3 months to the low dose arm of Acthar Gel (20-40 U QD). After repeated hospitalizations with severe respiratory symptoms, the infant died at (b) (6) months of age form respiratory failure and cardiac arrest.

One death was reported in the retrospective chart review (QSC007-ACT-002) from aspiration pneumonia possibly related to the "Other High Dose" dose category of Acthar Gel.

Postmarketing surveillance revealed eight other deaths. See 8.3 below.

7.3.2 Nonfatal Serious Adverse Events

Serous adverse events (SAEs) are defined as those requiring an emergency room visit and/or hospitalization. When the chart review of the patient did not indicate the spediifci condition requiring the emergency room visit or hospitalization, the SAE was coded as "emergency care examination" or "hospitalization" in the Sponsor's Table 1.6 reproduced below.

Table 1.6 Overall Summary of Serious Adverse Events by Treatment Group

Serious Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Patients with at least 1 SAE	**48 (35.8)**	**10 (7.5)**	**6 (11.5)**	**64 (20.1)**
Patients with No SAEs	**86 (64.2)**	**123 (92.5)**	**46 (88.5)**	**255 (79.9)**
Convulsion	17 (12.7)	1 (0.8)	0 (0.0)	18 (5.6)
Infections	11 (8.2)	2 (1.5)	3 (5.8)	16 (5.0)
Hypertension	10 (7.5)	2 (1.5)	0 (0.0)	12 (3.8)
Hospitalization	6 (4.5)	0 (0.0)	0 (0.0)	6 (1.9)
Pyrexia	3 (2.2)	0 (0.0)	0 (0.0)	3 (0.9)
Diarrhea	1 (0.7)	1 (0.8)	0 (0.0)	2 (0.6)
Vomiting	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Emergency care examination	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Decreased appetite	1 (0.7)	1 (0.8)	0 (0.0)	2 (0.6)
Grand mal convulsion	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Myoclonic epilepsy	2 (1.5)	0 (0.0)	0 (0.0)	2 (0.6)
Dyspnea	1 (0.7)	0 (0.0)	1 (1.9)	2 (0.6)
Pneumonia aspiration	0 (0.0)	2 (1.5)	0 (0.0)	2 (0.6)
Respiratory failure	1 (0.7)	0 (0.0)	1 (1.9)	2 (0.6)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Cardiac hypertrophy	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Diarrhea hemorrhagic	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)

Serious Adverse Event	Questcor Recommended Dose[a] (n=134) n (%)	Other High Dose[a] (n=133) n (%)	Low Dose[a] (n=52) n (%)	All Patients[a] (N=319) N (%)
Gastroesophageal reflux disease	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Irritability	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatomegaly	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Herpes zoster	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Shunt infection	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Compression fracture	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Biopsy liver	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Acidosis	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Dehydration	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Osteoporotic fracture	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Complex partial seizures	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Partial seizures	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Status epilepticus	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Acute respiratory distress syndrome	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Pulmonary edema	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)
Skin discoloration	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
Exposure to communicable disease	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Brain operation	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.3)

a. Dose groups are defined in Section 1.3.

Source: Section 1.12.3, Table 6.12.6, CSR 222017-02, CSR QSC007-ACT-002, CSR 222017 05

7.3.3 Dropouts and/or Discontinuations

The Sponsor provided very limited data concerning drop-outs and discontinuations, presented only in the format of narratives from the four clinical studies discussed in section 7.1.1 of this review.

There was no safety data from pivotal study CSR 22017-01.

The narratives (derived from retrospective chart reviews) from study CSR 22017-02 are often not clear as to whether discontinuations were planned or due to noncompliance or an adverse effect. Most of these patients were not in a clinical study,

The narratives (derived from retrospective chart reviews) from study CSR 22017-05 (Hrachovy 1994) indicated that two of the original 59 patients randomized dropped out

before receiving any Acthar Gel (as discussed previously, the safety population was 57). Of the 57 patients, only two narratives indicated discontinuation due to an adverse effect: patient 098-50 (increased blood pressure on high dose).and patient 090-008 (pyrexia on low dose). One patient (090-002) moved to Ohio. One patient (090-007) was lost to follow-up after one dose of low dose. It is not clear why the other three other patients discontinued the study.

The narratives (derived from retrospective chart reviews) from study CSR QSC007-ACT-002 are often not clear as to whether discontinuations were planned or due to noncompliance or an adverse effect. Most of these patients were not in a clinical study,

Patients from study CSR 22017-04 were not included in the integrated summary as previously discussed.7.3.4 Significant Adverse Events
The Sponsor's Table 6.12.4 (reproduced below) shows treatment-emergent adverse effects with an incidence greater than or equal to 2%.

Integrated Summary of Safety for HP Acthar Gel
NDA Supplement for the Treatment of Infantile Spasms

Table 6.12.4 Summary of Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2% by MedDRA System Organ Class by Preferred Term by Treatment Group

	Recommended Dose (N=134)	Other High Dose (N=133)	Low Dose (N=52)	All Patients (N=319)
CARDIAC DISORDERS	5 (3.7%)	1 (0.8%)	1 (1.9%)	7 (2.2%)
ENDOCRINE DISORDERS	3 (2.2%)	25 (18.8%)	8 (15.4%)	36 (11.3%)
CUSHINGOID	3 (2.2%)	25 (18.8%)	8 (15.4%)	36 (11.3%)
GASTROINTESTINAL DISORDERS	8 (6.0%)	21 (15.8%)	7 (13.5%)	36 (11.3%)
DIARRHOEA	3 (2.2%)	7 (5.3%)	2 (3.8%)	12 (3.8%)
VOMITING	4 (3.0%)	5 (3.8%)	3 (5.8%)	12 (3.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	12 (9.0%)	34 (25.6%)	11 (21.2%)	57 (17.9%)
IRRITABILITY	8 (6.0%)	26 (19.5%)	8 (15.4%)	42 (13.2%)
PYREXIA	6 (4.5%)	8 (6.0%)	4 (7.7%)	18 (5.6%)
INFECTIONS AND INFESTATIONS	27 (20.1%)	32 (24.1%)	17 (32.7%)	76 (23.8%)
INFECTIONS	25 (18.7%)	32 (24.1%)	16 (30.8%)	73 (22.9%)
INVESTIGATIONS	8 (6.0%)	11 (8.3%)	2 (3.8%)	21 (6.6%)
WEIGHT GAIN	1 (0.7%)	7 (5.3%)	0 (0.0%)	8 (2.5%)
METABOLISM AND NUTRITION DISORDERS	9 (6.7%)	22 (16.5%)	4 (7.7%)	35 (11.0%)
INCREASED APPETITE	0 (0.0%)	12 (9.0%)	1 (1.9%)	13 (4.1%)
DECREASED APPETITE	3 (2.2%)	4 (3.0%)	1 (1.9%)	8 (2.5%)
NERVOUS SYSTEM DISORDERS	22 (16.4%)	8 (6.0%)	1 (1.9%)	31 (9.7%)
CONVULSION	17 (12.7%)	4 (3.0%)	0 (0.0%)	21 (6.6%)

Treatment groups defined by maximum dose: Recommended Dose = 150 Divided range from 135 through 160 U/m2/day divided, BID; Other High Dose (>= 80 U/m²/day) excludes the Recommended Dose; and Low Dose (<80 U/m²/day).
All Patients group = (Recommended Dose) + (Other High Dose) + (Low Dose).

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Integrated Summary of Safety for HP Acthar Gel
NDA Supplement for the Treatment of Infantile Spasms

Table 6.12.4 Summary of Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2% by MedDRA System Organ Class by Preferred Term by Treatment Group

	Recommended Dose (N=134)	Other High Dose (N=133)	Low Dose (N=52)	All Patients (N=319)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (3.7%)	14 (10.5%)	7 (13.5%)	26 (8.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.7%)	24 (18.0%)	6 (11.5%)	31 (9.7%)
ACNE	0 (0.0%)	10 (7.5%)	3 (5.8%)	13 (4.1%)
RASH	0 (0.0%)	7 (5.3%)	2 (3.8%)	9 (2.8%)
SURGICAL AND MEDICAL PROCEDURES	6 (4.5%)	0 (0.0%)	1 (1.9%)	7 (2.2%)
VASCULAR DISORDERS	13 (9.7%)	17 (12.8%)	5 (9.6%)	35 (11.0%)
HYPERTENSION	13 (9.7%)	16 (12.0%)	5 (9.6%)	34 (10.7%)

Treatment groups defined by maximum dose: Recommended Dose = 150 Divided range from 135 through 160 U/m2/day divided, BID; Other High Dose (>= 80 U/m²/day) excludes the Recommended Dose; and Low Dose (<80 U/m²/day).
All Patients group = (Recommended Dose) + (Other High Dose) + (Low Dose).

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7.3.5 Submission Specific Primary Safety Concerns

See discussion of limitations of the safety data quality in section3.1 of this review.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

See Section 7.3.4 of this review.

7.4.2 Laboratory Findings

The Sponsor did not provide an integrated summary of laboratory findings. These are discussed in section 7.1.1 of this review under the individual safety studies.

7.4.3 Vital Signs

The Sponsor did not provide an integrated summary of vital signs. These are discussed in section 7.1.1 of this review under the individual safety studies.

7.4.4 Electrocardiograms (ECGs)

ECGs were not routinely done in this infant population.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity
Not evaluated. No adverse reactions attributable to immunogenicity were reported.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events
See section 7.2.2 of this review

There is a trend for increased adverse effects for higher doses of Acthar Gel especially when given for a treatment period exceeding two weeks with a two week taper. However, dose dependent studies with a prospective collection safety data has not been done.

7.5.2 Time Dependency for Adverse Events
The Partikian (CSR 222017-02) study suggests that some of the steroid-related adverse effects (risk of serious infection, osteopenia) are more likely in treatment courses longer than 2 weeks treatment with 2 weeks for tapering. This is part of the rationale for the proposed dosage. However, the limited data available does not definitively establish the proposed dosage (high dose, short duration) as the optimal one.

7.5.3 Drug-Demographic Interactions
See current labeling.

7.5.4 Drug-Disease Interactions
See current labeling.

The safety data suggest that pre-existing hypertension, congenital infection, other chronic infection or impaired immune status, and some metabolic disorders may be relative contra-indications to the use of Acthar Gel for infantile spasms.

7.5.5 Drug-Drug Interactions
See current labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity
See current labeling.

7.6.2 Human Reproduction and Pregnancy Data
See current labeling

7.6.3 Pediatrics and Assessment of Effects on Growth

Infantile spasms is a pediatric indication. No assessment of effects on growth has been done.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The sponsor reports there have been no reports of death or symptoms from an acute overdose of Acthar in clinical studies or in the published literature.

There are no systematic studies on the optimal taper period and whether or not there is acute withdrawal and/or rebound from Acthar in the treatment of patients with IS. Like all drugs in the corticosteroid class, it is common practice to taper patients receiving Acthar for the treatment of IS to reduce the possible occurrence of AEs that might be related to abrupt Acthar withdrawal.

The taper regimen suggested by Questcor in the proposed product label is as follows: Taper the dose for 3 days 30 U/m2 in the morning; for 3 days 15 U/m2 in the morning; for 3 days 10 U/m2 in the morning; for 6 days 10 U/m2 every other morning.

7.7 Additional Submissions: Review of Safety from Published Literature

8 Postmarket Experience

Questcor reviewed and summarized postmarketing surveillance records for Acthar gel including AEs, SAEs, and deaths reported to New Drug Application (NDA) 08-372 from 29 April 1952, when Acthar was approved, through June 2009. This review included all annual reports, periodic AE reports, 15-day alerts, and all follow-up reports submitted to FDA and any other NDA communications and submissions. A summary of the findings related to the safety of Acthar in treating IS reported in postmarketing surveillance records can be found in Section 1.5.2.

Safety data provided in this submission include data from postmarketing surveillance records for Acthar used to treat infants (Questcor Safety Database).

In support of this Complete Response, Questcor thoroughly reviewed in-house safety data for Acthar and AEs reported to NDA 08-372 from 29 April 1952, when the NDA for Acthar was approved, through June 2009. This review included all annual reports, periodic AE reports, 15-day alerts, and follow-up reports submitted to the FDA. Other NDA communications and submissions were also reviewed.

A review of all identified AEs was conducted for patients who had been treated with Acthar or unidentifiable ACTH for the indication of IS, and patients identified as infants by age (28 days through 24 months). In addition to IS, the terms implying the same disorder or a similar condition, such as hypsarrhythmia and myoclonic seizures, were included, in order to obtain the relevant postmarketing information. In these AE reports, the terms originally used to report the AEs were reproduced verbatim or were coded to the preferred term.

8.1 Postmarketing Surveillance Adverse Events Reported for Patients Treated with Acthar

Postmarketing surveillance records (Questcor Safety Database) show a total of 76 patient reports received by the manufacturers and submitted to the FDA for infants treated with Acthar, who experienced 1 or more AE(s).

The most commonly occurring AEs (>2 patients) observed in the postmarketing use of Acthar for the treatment of IS are summarized in the Sponsor's Table 1.8. This table is derived from a tabular summary of all postmarketing AEs provided in Appendix 1.12.5, Table 1.19. A detailed listing of patients and AEs can be found in Appendix 1.12.5, Table 1.18; the list is organized by the date the case was submitted to the NDA.

Table 1.8 Most Common (>2 Patients) AEs Reported to Manufacturer in Infants Treated with Acthar

Body System/Adverse Events (verbatim term)	No. of Patients Reporting AE
Endocrine disorders	
Cushing's syndrome	4
Facial edema	2
Gastrointestinal disorders	
Abdominal distention	2
Vomiting	2
General disorders and administration site conditions	
Drug withdrawal reaction	2
Edema	2
Fever	4
Ineffective therapy	3
Lethargy	2
Infections and infestations	
Oral thrush	2
Sepsis	4
Investigations	
Weight gain	2
Metabolism and nutrition disorders	
Appetite suppression	2
Dehydration	3
Fluid retention	2
Hypokalemia	3
Metabolic alkalosis	3
Nervous system disorders	
Insomnia	2
Seizure	4
Psychiatric (psychic) disorders	
Crying	2
Irritability	5
Respiratory disorders	
Cough	2
Pneumocystis carinii pneumonia	5
Respiratory distress	2

Body System/Adverse Events (verbatim term)	No. of Patients Reporting AE
Skin and subcutaneous tissue disorders	
Acne	2
Rash	6
Vascular disorders	
Hypertension	6

Notes: One patient may have more than one AE. Only one occurrence of an AE was counted for each patient. Adverse events were retrieved verbatim. No recoding was performed.

8.2 Postmarketing Surveillance Serious Adverse Events Reported for Infants Treated with Acthar

Thirty-three of the AE reports received by the manufacturers concerning the use of Acthar in infants were considered serious; these events were submitted to the FDA in 15-day alert reports (serious and unexpected or unlabeled events) or in periodic ADE reports (serious and expected or labeled events). A summary of the SAEs can be found in The Sponsor's Table 1.9.

Table 1.9 Serious Adverse Events Spontaneously Reported for Infants Treated with Acthar

Control No.	Dosing	Serious Adverse Events
M-335	80 U/d	Sepsis[a]
M-339	80 U/d	Sepsis[a]
M-340	80 U/d	Sepsis[a]
M-341	80 U/d	Sepsis[a]
M-342	80 U/d	Hypertension, metabolic alkalosis[a]
M-343	80 U/d	Hypertension, metabolic alkalosis[a]
M-344	80 U/d	Hypertension, metabolic alkalosis[a]
01-001174	150 U/m^2/d –IM Treatment Duration: 3 d Total Dose: 100.8 U	Pyruvate carboxylase deficiency, catastrophic metabolic acidosis, death[b]
01-001652	10 U/kg/d Treatment Duration: 21 d Total Dose: 1764 U	Cushing's ulcer, small fontanel, toxic appearance, abdominal distention, emesis, respiratory distress, fever[b]
01-000941	60 U/d Treatment Duration: 45 d Total Dose: 2700 U	Hypertension, weight gain, motor development delayed
01-008741	50 U/d to 25 U/d Treatment Duration: 30 d Total Dose: 1125 U	Soft/white gums, fever, respiratory failure, seizure, sore throat, death[b]

Control No.	Dosing	Serious Adverse Events
US01-08623/01-011039	56 U/day –IM Treatment duration: 68 d Total dose: 3808 U	Drug withdrawal reaction, appetite suppression, dehydration
US01-08028/01-011040	56 U/day –IM Treatment duration: 81 d Total dose: 4536 U	Drug withdrawal reaction, appetite suppression, dehydration
US01-19053	18 U/day –IM Treatment duration: 7 d Total dose: 126 U	Fever, seizures
US01-19351	20 U/d x 14 d 40 U/d x 14 d 80 U/d x 7 d 40 U/d x 7 d 40 U/qod x 10 d Treatment duration: 52 d Total dose: 1880 U	*P. carinii* pneumonia, septic shock, fluid retention, weight gain, acute tubular necrosis, hypernatremia, hypokalemia, urinary tract infections
US01-19376	70 U/day –IM Treatment duration: 120 d Total dose: 8400 U	*P. carinii* pneumonia, tachypnea, dyspnea, Cushing's syndrome, oral thrush[b]
US01-19380	40 U/day –IM Treatment duration: 90 d Total dose: 3600 U	Cough, respiratory distress, Cushing's syndrome, oral thrush, *P. carinii* pneumonia[b]
US01-19381	80 U/qod – IM Treatment duration: 210 d Total dose: 8400 U	Cough, rhinorrhea, decreased appetite, lethargy, Cushing's syndrome (obesity with acne, hirsutism, purple striae, respiratory distress, hypotonia), *P. carinii* pneumonia, death[b]
US01-19689	80 U/qod x 60 d 80 U/d x 90 d Treatment duration: 150 d Total dose: 9600 U	Mucocutaneous candidiasis, hypertension, bilateral severe pneumonia. (Pneumocystis organisms observed at autopsy), death[b]
US01-20092	20 bid to 30 bid, tapering Treatment duration: 32 d Total dose: 1640 U	Adrenal insufficiency, hypokalemia, cardiac arrest, anoxic brain injury
US01-20137	60 U/d x 21 d 40 U/d x 21 d 20 U/d x 14 d Treatment duration: 21 d to AE + 35 days Total dose: 1260 U to AE + 1120 U	Cardiac hypertrophy, hypertension, right upper lobe pneumonia, pulmonary edema, death[b]
US01-22284	80 U/day – IM Treatment duration: 42 d Total dose: 3360 U	Lethargy, decreased oral intake, rapid respiratory rate, *P. carinii* pneumonia[c]

Control No.	Dosing	Serious Adverse Events
US01-24280	80 U/d x 14 d 120 U/d x 14 d 80 U/d x 14 d 60 U/d x 35 d Treatment duration: 77 d Total dose: 4420 U	Respiratory syncytial virus infection, shortness of breath, fever, interstitial pneumonitis
2000-20713US	40 U bid Treatment duration: 153 d Total dose: 12240 U	Brain shrinkage[c], hydrocephalus
ACT-S0001	30 IU/mL qod – IM Treatment duration: NR	Hypertension, cardiomyopathy
03-ADE-SU-0001-ACT	32 - 16 U/mL qod – IM Treatment duration: NR	Seizure, death
03-ADE-SU-0002-ACT	40 U/d to 20 U/d – IM Treatment duration: NR	Vomiting, respiratory arrest, death[b]
06-ADE-SU-0017-ACT	150 U/m^2/d IM x 2 wk, taper x 2 wk Treatment duration: NR	Encephalitis herpes, disease recurrence
06-ADE-SU-0020-ACT	NR	*P jirovecii* pneumonia
07-ADE-SU-0012-ACT	40 U IM qd Treatment duration: NR	Irritability, convulsions
08-ADE-SU-0003-ACT	40 U IM qd for 6 wks with taper Treatment duration: NR	Dehydration, oral intake reduced, fluid retention, acne
09-ADE-SU-0013-ACT	20 - 40 U IM qd Treatment duration: 43 d	Bronchiolitis, acute respiratory distress syndrome
09-ADE-SU-0011-ACT	NR	Leukemia

Notes:
Reference: Table 1.20 - Listing of SAEs Reported to the Manufacturer in Infants treated with Acthar
NR = Not Reported, IM =Intramuscular; d = day, qd = once/day

a. From 15-day alert and MedWatch forms submitted to FDA. By current reporting standards, these did not meet the current criteria for reportable events, because inadequate information was in the original reports sent to the manufacturer.

b. Report derived from a case described in the medical literature; deaths in literature not listed in Table 1.20: 01-001174, 01-008741, and 03-ADE-SU-0002-ACT.

c. The term brain shrinkage was used here, instead of cerebral atrophy.

8.3 Postmarketing Surveillance Deaths

Eight deaths were reported previously to NDA # 08-372 as part of ongoing postmarketing surveillance and are presented in the Sponsor's Table 1.10.

Table 1.10 Postmarketing Surveillance Summaries of Deaths Reported for Infants Treated with Acthar

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
13-Apr-90	01-001174[b]	150 U/m^2/day –IM Treatment duration: 3 d Total dose: 100.8 U[c]	The patient died at 12 weeks of age after recurrent episodes of profound acidosis. At autopsy, the brain manifested cystic degeneration and demyelination. According to the reporter, the dramatic rise in alanine levels coincident with ACTH therapy suggests that ACTH played a role in precipitating the catastrophic metabolic acidosis. The patient's physician stated that the infant was symptomatic before ACTH therapy and felt that ACTH may have exacerbated the reaction, but did not cause it. The event report included no opinion regarding a possible causal relationship between the events and Acthar treatment.
05-Oct-95	01-008741	50 U/day to 25 U/d Treatment duration: 30 d Total dose: 1125 U[d]	She experienced seizures while being treated with Acthar, the dose was decreased to 25 U daily and, according to the patient's father, the seizures worsened. The treatment duration at this time was 1 month. The patient was hospitalized with fever and a sore throat, administered oxygen through an oxygen tube, but without effect, and subsequently died. The cause of death reported by the pathologist was neurofibromatosis.
23-Jul-98	US01-19381[b]	80 U/qod – IM Treatment duration: 210 d Total dose: 8400 U	Because of rapid deterioration in respiratory status, trimethoprim-sulfamethoxazole 20 mg/kg/d was administered intravenously and mechanical ventilation started. Tissue from an open-lung biopsy showed severe alveolar damage with hyaline membranes, interstitial fibroblastic proliferation, and the presence of *P. carinii*. Cytomegalovirus was subsequently recovered from cultures of the lung specimen. The patient's condition continued to deteriorate, and he died 10 d after admission.
02-Sep-98	US01-19689[b]	80 U/qod x 60 d 80 U/d x 90 d Treatment duration: 150 d Total dose: 9600 U	Seizures ceased within 4 d. Two months later, seizures recurred, and the Acthar dosage was increased to 80 U/d. Seizure frequency declined, but the patient developed mucocutaneous candidiasis that responded poorly to topical therapy, and he became hypertensive. After 3 months, oral prednisone 1 mg/kg/d was substituted for Acthar with the intent of tapering. Clonazepam was used for seizure control. Two d later, the patient's mother thought he was "congested." The next day, the patient was found dead in his crib. The postmortem examination revealed bilateral severe pneumonia.

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
28-Oct-98	US01-20137[b]	60 U/d x21 d 40 U/d x 21 d 20 U/d x 14 d Treatment duration: 21 d to AE + 35 d, total treatment was 8 weeks. Total dose: 1260 U to AE + 1120 U	The seizures ceased within 24 hours. Three weeks later, examination revealed severe peripheral edema, tachypnea, hypertension (174 mm Hg systolic), hepatomegaly, and intermittent apnea. The Acthar dose was reduced to 40 U/d, and the systolic blood pressure gradually decreased to 110 mm Hg. An ECG conducted 6 weeks after institution of ACTH revealed no change in the degree of septal and left ventricular freewall hypertrophy, or systolic anterior motion of the mitral valve. The dose of Acthar was reduced to 20 U/d with no return of seizure activity. Cardiomegaly and edema persisted. 8 weeks after the start of Acthar, while at home, the infant became lethargic and pale and died during a nap. Postmortem examination revealed bilateral pulmonary edema, right upper lobe pneumonia, centrilobular hepatic congestion, and periventricular leukomalacia. The heart had severe asymmetric left ventricular hypertrophy without dilation of the chambers.
29-May-03	03-ADE-SU-0001-ACT	16 -32 U/mL qod – IM Treatment duration: NR	The medical history included hypertension. The patient was at home and had responded well to Acthar, with cessation of spasms. At the time of the event, the patient was on a tapering regimen of the drug. According to her family the patient had a uniquely new seizure, stopped breathing, and died suddenly. She could not be resuscitated. The treating physician did not think that Acthar was the cause of the event. The patient was severely neurologically impaired.
29-May-03	03-ADE-SU-0002-ACT	40 U alternating with 20 U qod – IM Treatment duration: NR	The patient was at home, and had responded well to a stable regimen of Acthar, with cessation of spasms. The patient became unresponsive after vomiting, had a respiratory arrest, and could not be resuscitated. The physician considered Acthar unrelated to the event. The patient was severely neurologically impaired. Preliminary verbal autopsy indicated impressive right ventricular hypertrophy, and the brain showed evidence of hypoxic ischemic changes before death. The final autopsy report included no information that would indicate relation of the event to treatment. The most likely cause of death was the patient's congenital cardiac and central nervous system abnormalities.

Report Date	Control No.	Acthar Dose	Key Verbatim Excerpts from SAE Narratives[a]
05 May 09[d]	09-ADE-SU-0013-ACT	20 - 40 U IM qd Treatment duration: 43 d	The patient was a 3.3-month-old male infant with a history of IS, microcephaly, and severe developmental delay at the time treatment with Acthar low-dose (20 U/qd) began on (b) (6). On (b) (6) the dose of Acthar was increased to 30 U/qd per protocol as the patient continued to have spasms. On (b) (6) the patient was admitted to the (b) (6) with bronchiolitis, acute respiratory distress syndrome, and pneumonia: a diagnosis of RSV was made. The patient improved and was discharged on (b) (6) the records of that admission show that the Acthar dose was 30 U/day. On (b) (6), the patient was readmitted with worsening respiratory symptoms; the records of this admission note the Acthar dose was 40 U/day. The patient improved and was discharged on (b) (6) the dose of Acthar was scheduled to be tapered to 20 U/qd per a note in the patient chart at (b) by the investigator; however, there is no documentation that this lower dose was ever administered. On (b) (6), the patient was again admitted to the (b) (6) with continuing respiratory symptoms. Despite aggressive care and antibiotic therapy, the patient developed pulmonary edema, respiratory failure, and died of cardiac arrest on (b) (6); the patient was (b) months of age at the time of death. The dose of Acthar at this last admission was not documented. The investigator did not assess the relationship of these SAEs to Acthar.

a. This column contains information excerpted verbatim from the SAE narratives of the events that had outcomes of death. Causes of death and physicians' comments about the causality relationships between the death and Acthar or ACTH are included when these data were available.

b. Report derived from a case described in medical literature.

c. Duration per regimen not reported. Total dose assumes 2 weeks at initial dose (50 U), 2 weeks at tapered dose (25 U)

d. Report documented in CSR 222017-05 and submitted via MedWatch.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-432 / N_000
Drug Name:	H.P. Acthar Gel (repository corticotropin injection)
Indication(s):	Infantile Spasms
Applicant:	Questcor Pharmaceuticals
Date(s):	Date of Document: December 10, 2009
	PDUFA due date: June 10, 2010
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D.
	Kooros Mahjoob, Ph. D.
Medical Division:	Division of Neuropharmacological Drug Products, HFD-120
Clinical Team:	Philip Sheridan, M.D.
Project Manager:	Susan Daugherty, Pharm.D.
Keywords:	Sample size, retrospective

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor obtained source efficacy data from three published, randomized, controlled studies. Among three studies, Study 222017-01 showed that Acthar Gel was significantly better than prednisone in both EEG response and clinical seizure response as well as the overall response ($p<0.01$). Study 222017-05 had 59 patients enrolled in the trial but a number of patients did not complete the study protocol, which had a considerable impact on the results of the trial. Depending on the population used for analyses, the conclusion can vary. Study 222017-04 compared Acthar low-dose with prednisone and showed that the low dose did not differ much from prednisone numerically ($p>0.99$).

Even though Study 222017-01 showed highly significant treatment effect of Acthar Gel, it is somewhat concerning that the conclusion cannot be directly confirmed in the other two trials. The analyses are retrospective and the sample size in each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. The data to draw a definitive conclusion are limited. The efficacy evidence from three trials needs to be weighted carefully.

1.2 Brief Overview of Clinical Studies

The sponsor presented the efficacy results based on 3 published, randomized controlled trials (RCTs) where Acthar was evaluated for the treatment of patients with infant spasms (Baram 1996, Hrachovy 1994, Hrachovy 1983).

Study 222017-01 (Baram 1996) is a single-blind study compared high dose Acthar (150 U/ m^2/day) administered twice daily and prednisone (2 mg/kg/day) administered twice daily in patients with IS. 15 patients were randomized to Acthar and 14 patients were randomized to prednisone.

Study 222017-05 (Hrachovy 94) is a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen (150 U/m^2/qd) to Acthar low-dose regimen (20 U/qd) in patients with IS. 59 patients were enrolled in the study. 9 patients did not complete the treatment protocol.

Study 222017-04 (Hrachovy 83) is a randomized, controlled, double-blind study that compared low dose Acthar (20 to 30 U/day) administered as a single daily dose to prednisone at a dose of 2 mg/kg/day in patients with IS. 12 patients were randomized to Acthar Gel and 12 were randomized to prednisone.

1.3 Statistical Issues and Findings

Unlike the conventional pivotal trials submitted for drug approvals, the efficacy evidence of Acthar gel in treating infantile spasms is based on three published randomized controlled trials. Although the sponsor obtained the source efficacy data of those three trials and re-analyzed them, there was no prospectively defined statistical analysis plan. The sample size of each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. Therefore the efficacy data to draw conclusions are limited. Even though the sponsor used one study (222017-04) as the pivotal trial and the other two as supportive trials, this was not determined prospectively. All three studies should be weighted carefully. Furthermore, the so-called primary endpoint may not carry as much weight as the primary endpoint in the conventional clinical trials since it was not defined prospectively.

Study 222017-05 had a number of patients who did not complete the treatment protocol. Depending on the population used for analyses, the conclusion can vary. The analyses of overall response and EEG response showed no statistically significant differences between the 2 treatment groups. The analysis of the spasm control response by IS etiology showed a nominally significant difference between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose. This is based on the sponsor-defined mITT population. The significance disappeared if some other defined population is used (e.g., ITT population, completed patients population). Study 222017-04 showed similar overall response rate in both Acthar low-dose group and prednisone group. It cannot be determined whether it suggests that the low dose Acthar has similar effect in treatment infantile spasms as prednisone, or it is likely due to the small sample size of the trial.

2. INTRODUCTION

2.1 Overview

Out of 5 published, randomized controlled trials (RCTs) where Acthar was evaluated for the treatment of patients with infant spasms, the sponsor was able to obtain source efficacy data from the following 3 studies:

- Questcor obtained source efficacy data from the study conducted by Dr. Baram (Baram 1996). Questcor's analyses of these data are presented as CSR 222017-01. CSR 222017-01 is designated as the pivotal efficacy study.

- Questcor obtained source efficacy data from the 2 additional RCTs conducted and published by Dr. Hrachovy and colleagues (Hrachovy 1994, Hrachovy 1983). Questcor's analyses of these data are presented as CSR 222017-05 and CSR 222017-04, respectively. CSR 222017-05 is presented as the supportive efficacy study. Additional efficacy data supporting the use of Acthar for the treatment of IS patients is presented in CSR 222017-04.

Pivotal study 222017-01 is a single-blind comparison of response to treatment. It compared Acthar 150 U/ m^2/day administered as 75 U/ m^2/bid IM for 2 weeks with a taper to zero for an additional 2 weeks and prednisone 2 mg/kg/day administered as 1 mg/kg/bid orally (PO) for 2 weeks with a taper to zero over 2 weeks in patients with IS. 15 patients were randomized to Acthar and 14 patients were randomized to prednisone.

The supportive efficacy study 222017-05 is a prospective, controlled, randomized, single-blind study that compared an Acthar high-dose regimen (150 U/ m^2/qd) to Acthar low-dose regimen (20 U/qd) in patients with IS. The study enrolled 59 patients (30 in high-dose, 29 in low-dose). Nine patients (4 in the high-dose group, 5 in the low-dose group) did not complete the treatment protocol.

Study 222017-04 is a randomized, controlled, double-blind study that compared Acthar at a dose of 20 to 30 U/day administered as a single daily (20 to 30 U/qd) IM dose (Acthar low-dose) to prednisone at a dose of 2 mg/kg/day PO in patients with IS. 12 patients were randomly assigned to Acthar Gel and 12 were randomly assigned to prednisone.

2.2 Data Sources

The sponsor's electronic submission is stored under the directory of
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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY 222017-01

3.1.1.1 Study Objectives

The objective of this study was to compare the efficacy of H.P.Acthar Gel (repository Corticotropin injection or ACTH) 150 U/m^2/day and prednisone (2 mg/kg/day), administered for 2 weeks, in suppressing clinical spasms and hypsarrhythmic electroencephalogram (EEG) in patients with infantile spasms (IS).

3.1.1.2 Study Design

The study was initially designed as a single-blind comparison of response to treatment, evaluating a single dose of ACTH 20 U/day compared to ACTH 150 U/m^2/day and to prednisone (2g/kg/day) in the treatment of infants with IS. Acthar 150 U/m2/day was administered as 75 U/m2/bid IM for 2 weeks and then tapered to zero for an additional 2 weeks. Prednisone 2 mg/kg/day was administered as 1 mg/kg/bid PO for 2 weeks, and then tapered to zero over 2 weeks. The study was amended to eliminate the 20 U/day ACTH dose. As a result of the amendment, the study was a single-blind comparison of response to treatment, evaluating 150 U/m2/day ACTH and 2mg/kg/day prednisone in the treatment of infants with IS. The investigators were unblinded to the treatment assignment but the interpreter of the video -EEG was blinded. Patients with persistent spasms or hypsarrhythmia after initial treatment were offered the alternative treatment.

Patients eligible for enrollment into this study were diagnosed with clinical IS. An infant previously treated with any steroid or Acthar treatment was not eligible for the study. All patients had a 24-hour video-EEG to ascertain the presence of hypsarrhythmia before initiation of treatment. Seizure frequency was monitored throughout the 2-week treatment period by parents who maintained seizure diaries. After 2 weeks of treatment, a repeat video-EEG was performed, and both clinical and EEG responses were assessed. Video-EEG monitoring was performed for a minimum of 4 hours and optimally, for 24 hours and included a minimum of 1 full sleep-wake cycle.

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

Since this is re-analysis of a published study, the sponsor did not specify primary or secondary endpoints. The endpoints were referred as efficacy endpoints. The efficacy measure of the study was a combined clinical (seizure) and video-EEG response, which was used to establish response to treatment. In addition, the sponsor also provided analysis of response adjusted for age as well as the analysis of response to crossover treatment.

(2) Secondary Efficacy Endpoints

Not applicable.

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Fifteen (15) patients were randomized to Acthar and 14 patients were randomized to prednisone.

Table 1 Summary of Demographic and Baseline Characteristics

	Prednisone N[a]=14	Acthar Gel N=15	All Patients N=29	*P*-value
Age, months[b]				0.0616
Mean	7.5	5.1	6.3	
SD	4.51	2.21	3.66	
Median	7.0	5.0	6.0	
Min, Max	3, 21	2, 11	2, 21	
Gender, n[a] (%)[c]				0.0959
Female	6 (42.9)	11 (73.3)	17 (58.6)	
Male	8 (57.1)	4 (26.7)	12 (41.4)	
Etiology Category, n (%)[c]				0.9408
Symptomatic	12 (85.7)	13 (86.7)	25 (86.2)	
Cryptogenic	2 (14.3)	2 (13.3)	4 (13.8)	

a. N/n is the number of patients.
b. The comparison of age distributions between treatment groups was performed with a Mann-Whitney test.
c. The comparisons of gender and etiology category frequencies by treatment were performed with a Pearson chi-square test.

[Source: Sponsor's clinical study report 222017-01 Table 11.1, confirmed by the reviewer]

3.1.1.5 Sponsor's Primary Efficacy Results

As mentioned previously in Section 3.1.1.3, the sponsor did not specify primary or secondary endpoints. So the reviewer also referred the analyses as efficacy analyses. For a patient to be considered a responder to treatment, both video-EEG and clinical (seizure) responses were necessary. The sponsor reported that the overall response (ie, EEG plus clinical response) indicated greater efficacy of Acthar Gel (13/15, 86.7%) compared to prednisone (4/14, 28.6%), *P*=0.0015.

Table 2 Analysis of Response to Treatment

	Prednisone N=14	**Acthar Gel N=15**	***P*-value**
Overall Response (EEG + Clinical), n (%)			0.0015
Yes	4 (28.6)	13 (86.7)	
No	10 (71.4)	2 (13.3)	
EEG Response, n (%)			0.0015
Yes	4 (28.6)	13 (86.7)	
No	10 (71.4)	2 (13.3)	
Clinical Response, n (%)			0.0003
Yes	4 (28.6)	14 (93.3)	
No	10 (71.4)	1 (6.7)	

* p-value is based on Pearson Chi-square test
[Source: Sponsor's clinical study report 222017-01 Table 11.2, confirmed by the reviewer]

The sponsor performed analyses of response to treatment adjusted for age group for the overall, EEG, and clinical response. Each analysis to evaluate the relative response rate (risk) for ACTH compared to prednisone was stratified by age at 2 levels. The analysis was performed for age groups defined by thresholds at 5, 6, 7, 8, 9, or 10 months. The sponsor reported that the differences between ACTH and prednisone for EEG and clinical responses remained statistically significant favoring the ACTH treatment group after adjusting for age group ($P<0.01$, for all comparisons).

Table 3 Analyses of Overall Response to Treatment Adjusted for Age

Age Groups (Months)	N	Response	Treatment: Prednisone (N=15)	Treatment: ACTH (N=14)	Weighted Relative Risk (95% CI)	P-value (d)
< 5	9	Yes	0 (0.0%)	5 (83.3%)	3.37 (1.32, 8.58)	0.0015
		No	3 (100%)	1 (16.7%)		
>=5	20	Yes	4 (36.4%)	8 (88.9%)		
		No	7 (63.6%)	1 (11.1%)		
< 6	14	Yes	0 (0.0%)	7 (77.8%)	3.81 (1.44, 10.09)	0.0006
		No	5 (100%)	2 (22.2%)		
>=6	15	Yes	4 (44.4%)	6 (100%)		
		No	5 (55.6%)	0 (0.0%)		
< 7	19	Yes	1 (16.7%)	11 (84.6%)	3.95 (1.26, 12.38)	0.0017
		No	5 (83.3%)	2 (15.4%)		
>=7	10	Yes	3 (37.5%)	2 (100%)		
		No	5 (62.5%)	0 (0.0%)		
< 8	21	Yes	2 (25.0%)	11 (84.6%)	3.27 (1.28, 8.37)	0.0021
		No	6 (75.0%)	2 (15.4%)		
>=8	8	Yes	2 (33.3%)	2 (100%)		
		No	4 (66.7%)	0 (0.0%)		

[Source: Sponsor's clinical study report 222017-01 Section 14.2 Table 3, confirmed by the reviewer]

The p-values in the tables were calculated based on Mantel-Haenszel test by controlling the age factor. The weighted relative risk is obtained from the Estimate of the Common Relative Risk (Row1/Row2) in SAS.

Assuming that the true prednisone response rate is 28.6%, as observed in the current study, the sponsor suggested that a future study, with 15 subjects randomized to Acthar Gel and 14 to prednisone would have at least 80% power to detect a treatment difference if the true Acthar Gel response rate is at least 84.4%. The study had only 10% power to detect a 20% difference in response rates compared between treatments.

Patients were also followed up for an average of 15 months (minimum of 1 month and maximum of 48 months).

3.1.1.6 Sponsor's Secondary Efficacy Results

Not applicable.

3.1.1.7 Reviewer's Results

The reviewer confirmed sponsor's analyses of response to treatment. Due to the small numbers in each cell, it would be more appropriate to use Fisher's Exact test instead of Chi-square test to compare the response rates between Acthar Gel group and prednisone group. The results based on Fisher's Exact test are shown in the following table (Table 4). The results do not differ much from the sponsor's results.

Table 4 Analysis of Response to Treatment using Fisher's Exact Test

	Prednisone	Acthar Gel	p-value
Overall response			0.0025
Yes	4	13	
No	10	2	
EEG response			0.0025
Yes	4	13	
No	10	2	
Clinical Response			0.0005
Yes	4	14	
No	10	1	

The median follow up time in this study is 11 months and mean follow up time is 15.3 months. The minimum and maximum follow up time for the 29 patients are 1 month and 48 months, respectively. 1 patient was recorded to have relapse in the sponsor's dataset.

3.1.1.8 Conclusions

Pivotal study 222017-01 appears to show that Acthar was superior to prednisone in infant spasms using twice-daily administration and 2-week high-dose regimen with a 2-week taper.

3.1.2 STUDY 222017-05

3.1.2.1 Study Objectives

The primary objectives of this study analysis were to compare the efficacy and safety of Acthar high-dose with that of Acthar low-dose in the treatment of patients with infantile spasms (IS). The secondary objective of this study analysis was to assess efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

3.1.2.2 Study Design

This is a randomized, controlled, single-blind study of Acthar high-dose (150 U/m2/once-daily [qd]), long-duration (3 weeks treatment plus 9 weeks taper) versus Acthar low-dose (20 U/qd), short-duration (2 to 6 weeks treatment plus 1 to 2 weeks taper) in patients with IS. Before initiation of treatment, each patient was monitored for up to 24 hours to confirm the presence of clinical spasms and to characterize the EEG pattern. At the end of the 12-week treatment period, patients returned for an EEG monitoring session to evaluate response to therapy. Developmental testing was repeated at this time. Nonresponders were treated with prednisone, 2 mg/kg/day for 4 to 6 weeks, and then followed in a routine clinical manner. Reviewers of the monitoring studies were unaware of the dosage of ACTH administered.

3.1.2.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy endpoint was the Overall Response. An Overall Response was defined as both cessation of spasms and resolution of the hypsarrhythmic EEG pattern at any time during the study.

(2) Secondary Efficacy Endpoints

The secondary efficacy endpoints were the assessment of efficacy based on spasm cessation alone (Spasm Control Response) and by resolution of the hypsarrhythmic EEG pattern (Hypsarrhythmia EEG Pattern Response) alone between the 2 treatment groups.

Note that the original publication (Hrachovy 1994) did not use primary and secondary endpoints.

3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

Fifty-nine (59) patients were enrolled in the study. In the original publication (Hrachovy 94), only 50 out of the 59 patients were included in the analysis. Nine patients (4 in the high-dose group, 5 in the low-dose group) were excluded because they did not complete the treatment protocol due to various reasons. Among the nine patients, information from eight patients was recovered. The sponsor subsequently included all patients in the analyses as requested by the Division.

Among the fifty-nine patients, thirty (30) patients were randomly assigned to the Acthar high-dose group and 29 were randomly assigned to the Acthar low-dose group. Twelve (12) patients were withdrawn from the study prior to completion of the protocol: 4 patients were withdrawn due to AEs, 1 patient was withdrawn due to death, and 7 patients were withdrawn due to another reason. The chart for 1 patient (90-999) could not be located; based on information provided by the investigator, this patient was randomly assigned to the Acthar low-dose group Two patients (90-005, 90-006) were randomized and assigned to treatment but did not receive any Acthar doses.

Table 5 Summary of Patient Disposition by Treatment Group (ITT Population)

Parameter	Acthar High Dose n=30	Acthar Low Dose n=29	Acthar All Patients N=59
Number of patients enrolled, n (%)	30 (100)	29 (100)	59 (100)
Number of patients completed, n (%)	25 (83.3)	21 (72.4)	46 (78.0)
Number of patients with no documentation, n (%)	0	1 (3.4)	1 (1.7)
Number of patients prematurely withdrew, n (%)	5 (16.7)	7 (24.1)	12 (20.3)
Number of patients withdrew due to AEs	1 (3.3)	3 (10.3)	4 (6.8)
Number of patients withdrew due to death	0 (0.0)	1 (3.4)	1 (1.7)
Number of patients withdrawn due to other reason	4 (13.3)	3 (10.3)	7 (11.9)

[Source: Sponsor's clinical study report 222017-05 Table 10.1, confirmed by the reviewer]

There are 4 efficacy analysis populations for this study. These were defined as follows:

The mITT Population (n=51) includes all patients who were randomized, received ≥ 1 dose of Acthar study medication, and had sufficient data to evaluate the Overall Response. This was sponsor's primary efficacy analysis population.

The ITT Population (n=59) includes all patients randomized to treatment. This population included the 1 patient who was randomized to Acthar low-dose whose chart was not able to be located by Dr. Hrachovy; this is the only population that includes this patient. The ITT Population was used to perform a sensitivity analysis of the treatment efficacy response. All patients with unknown Spasm Control Response or Hypsarrhythmic EEG Pattern Response were classified as responders if in the Acthar low-dose group, and as nonresponders if in the Acthar high-dose group.

The Spasms Population (n=55) includes all patients with sufficient data to evaluate the Spasm Control Response.

The Completed Patients Population (n=50) includes the 50 patients identified by the investigators as having completed the study protocol. The Completed Patients Population was analyzed for this report so that Questcor could perform an independent analysis of the same population of patients analyzed by the investigators. This population is identical to the one used in Hrachovy 94 publication. Note that the sponsor reported 46 patients who completed study in Table 5. The sponsor stated that it was unknown what criteria were used by Dr. Hrachovy in identifying the 50 patients in his analysis. No analysis was done on the 46 "completed patients" selected by the sponsor.

The Safety Population (n=57) includes all patients known to have been dosed with ≥ 1 dose of Acthar. Patients were classified by treatment. Safety summaries were based on the Safety Population.

Table 6 and Table 7 provide summary on analysis populations, as well as demographic and baseline statistics.

Table 6 Analysis Populations by Treatment Group

	Acthar High Dose n=30	**Acthar Low Dose n=29**	**Acthar All Patients N=59**
Populations for Analysis, n (%)			
ITT Population	30 (100.0)	29 (100.0)	59 (100.0)
mITT Population	24 (80.0)	27 (93.1)	51 (86.4)
Spasms Population	28 (93.3)	27 (93.1)	55 (93.2)
Completed Patients Population	26 (86.7)	24 (82.8)	50 (84.7)
Safety Population	28 (93.3)	29 (100)	57 (96.6)

[Source: Sponsor's clinical study report 222017-05 Table 10.2, confirmed by the reviewer]

Table 7 Summary of Demographic and Baseline Characteristics

Variable	Treatment Group: Acthar High Dose n=24	Acthar Low Dose n=27	Acthar All Patients N=51
Age at onset of spasms (months)			
n	24	26	50
Mean (SD)	8.05 (5.149)	9.07 (6.31)	8.58 (5.746)
Median	6.77	6.39	6.62
Min, max	1.9, 25.2	2.6, 28.2	1.9, 28.2
Age at start of treatment (months)			
n	24	26	50
Mean (SD)	8.25 (5.159)	9.31 (6.457)	8.8 (5.836)
Median	6.98	6.41	6.72
Min, max	1.9, 25.2	2.6, 28.2	1.9, 28.2
Sex, n (%)			
Male	12 (50.0)	19 (70.4)	31 (60.8)
Female	12 (50.0)	8 (29.6)	20 (39.2)
Race, n (%)			
White	9 (37.5)	11 (40.7)	20 (39.2)
Black or African-American	5 (20.8)	6 (22.2)	11 (21.6)
Unknown	9 (37.5)	7 (25.9)	16 (31.4)
Other	1 (4.2)	0 (0.0)	1 (2.0)
Etiology Category, n (%)			
Symptomatic	17 (70.8)	18 (66.7)	35 (68.6)
Cryptogenic	7 (29.2)	9 (33.3)	16 (31.4)

* one patient did not have data for age
[Source: Sponsor's clinical study report 222017-05 Table 10.3, confirmed by the reviewer]

3.1.2.5 Sponsor's Primary Efficacy Results

The Overall Response rate in the mITT Population (N=51) was 15/24 (62.5%) in the Acthar high-dose group and 13/27 (48.1%) in the Acthar low-dose group. The risk ratio was 1.318. However, the Overall Response rates between the 2 groups were not significantly different. The treatment comparison was *P*=0.2768.

The Overall Response rate in the ITT Population sensitivity analysis (N=59) was 15/30 (50.0%) in the Acthar high-dose group and 15/29 (51.7%) in the Acthar low-dose group. The risk ratio was 0.982. The Overall Response rates in the sensitivity analysis were not significantly different. The treatment comparison was *P*=0.9443.

The sponsor attributed the non-significant results of the trial to the once-daily administration of Acthar in this trial. In this study, Acthar was administered as a once-daily dose of 150 U/m^2. Although this daily dose was equivalent to the total daily dose in CSR 222017-01, the Acthar in the CSR 222017-01 was administered as 2 divided daily doses (ie, 75 U/m^2 per dose). The sponsor argued that this once-daily dosing could yield a lower ACTH accumulation when compared to the ACTH accumulation from twice-daily dosing.

3.1.2.6 Sponsor's Secondary Efficacy Results

The Spasm Control Response rate in the mITT Population (N=51) was greater in the Acthar high-dose group (19/24, 79.2%) than in the Acthar low-dose group (14/27, 51.9%). The risk ratio was 1.553 and the treatment comparison was *P*=0.0329.

The Hypsarrhythmic EEG Pattern Response rate in the mITT Population (N=51) was 16/24 (66.7%) in the Acthar high-dose and 14/27 (51.9%) in the Acthar low-dose groups. The risk ratio was 1.299 and the treatment comparison was *P*=0.2686.

The sponsor also performed a number of sensitivity analyses based on different populations as shown in Table 8, Table 9, and Table 10 (ITT population, spasm population, and completed patients population). The p-values were calculated based on Mantel-Haenszel test comparing response rates between treatments, stratified on etiology. The risk ratio is the common relative risk calculated by PROC FREQ procedure.

Table 8 Sensitivity Analyses in ITT Population (N=59)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	30	15 (50.0)	15 (50.0)	0.982	0.9443
	Low Dose	29	15 (51.7)	14 (48.3)		
Spasm Control Response	High Dose	30	23 (76.7)	7 (23.5)	1.410	0.0691
	Low Dose	29	16 (55.2)	13 (44.8)		
Hypsarrhythmic EEG Pattern Response	High Dose	30	16 (53.3)	14 (46.7)	0.865	0.5209
	Low Dose	29	18 (62.1)	11 (37.9)		

[Source: Sponsor's clinical study report 222017-05 Table 11.4, confirmed by the reviewer]

There were 4 patients in the low dose group who did not have complete EEG data and were therefore assigned as EEG responders in the ITT analysis (Patients 90-007, 90-008, 90-999, and 97-068).

Table 9 Sensitivity Analyses in Spasms Populations (N=55)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	28	15 (53.6)	13 (46.4)	1.133	0.6363
	Low Dose	27	13 (48.1)	14 (51.9)		
Spasm Control Response	High Dose	28	23 (82.1)	5 (17.9)	1.612	0.0126
	Low Dose	27	14 (51.9)	13 (48.1)		
Hypsarrhythmic EEG Pattern Response	High Dose	28	16 (57.1)	12 (42.9)	1.116	0.6580
	Low Dose	27	14 (51.9)	13 (48.1)		

[Source: Sponsor's clinical study report 222017-05 Table 11.5, confirmed by the reviewer]

Table 10 Sensitivity Analyses in Completed Patients Populations (N=50)

Outcome	Acthar Treatment	n	Responders n (%)	Nonresponders n (%)	Risk Ratio	*P*-value
Overall Response	High Dose	26	15 (57.7)	11 (42.3)	1.058	0.8225
	Low Dose	24	13 (54.2)	11 (45.8)		
Spasm Control Response	High Dose	26	21 (80.8)	5 (19.2)	1.374	0.0782
	Low Dose	24	14 (58.3)	10 (41.7)		
Hypsarrhythmic EEG Pattern Response	High Dose	26	16 (61.5)	10 (38.5)	1.050	0.8349
	Low Dose	24	14 (58.3)	10 (41.7)		

[Source: Sponsor's clinical study report 222017-05 Table 11.6, confirmed by the reviewer]

3.1.2.7 Reviewer's Results

The reviewer is able to confirm the results reported by the sponsor. The reviewer compared response rates across all three trials (Table 11). While the response rates in prednisone group and in ACTH low dose group vary in different trials, the response rates in ACTH high dose group differ the most across trials. The response rate in ACTH high dose group is much lower in Study 222017-05 than in Study 222017-01. One possible explanation of the rate difference could be due to the once-daily dosing versus the twice-daily dosing and this would be agreeable to the sponsor's argument.

3.1.2.8 Conclusions

The efficacy results in Study 222071-01 cannot be confirmed in this trial. The analysis of Overall Response (spasms cessation and resolution of the hypsarrhythmic pattern on EEG) showed no statistically significant differences between the 2 treatment groups in any of the 4 defined populations. The analysis of the Spasm Control Response by IS etiology, however, showed a nominal statistical significance between the Acthar high-dose and Acthar low-dose treatment groups in favor of Acthar high-dose (P=0.0329) based on the sponsor-defined mITT population.

Even though this is the largest study among three studies included in this application, the sample size is still small. The study can be underpowered. The different administration of ACTH (twice-daily in Study 222017-01 versus once-daily in Study 222017-05) may have effect on the outcome; however, it cannot be proven definitively. The efficacy results of this study remain inconclusive.

Table 11 Comparison of Response Rates across All Three Studies

	Acthar Gel						prednisone		
	High dose			Low dose					
Study	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)	overall response rate (%)	EEG response rate (%)	clinical response rate (%)
222017-01	86.7	86.7	93.3	NA	NA	NA	28.6	28.6	28.6
222017-05*	62.5	66.7	79.2	48.1	51.9	51.9	NA	NA	NA
222017-04**	NA	NA	NA	41.7	75.0	41.7	33.3	41.7	33.3

* Based on mITT population defined by the sponsor

** The response rates are calculated using initial stage only

3.1.3 STUDY 222017-04

3.1.3.1 Study Objectives

The primary objective of this study was to compare the efficacy of H.P. Acthar Gel (repository corticotropin injection) (20 to 30 U/day) with prednisone (2 mg/kg/day) in treating infantile spasms (IS).

3.1.3.2 Study Design

This is a double-blind crossover study of Acthar Gel or prednisone therapy in patients with IS. After completion of a baseline 24 to 48-hour monitoring period to confirm the presence of IS and to establish a baseline seizure frequency, patients were randomly assigned to receive Acthar Gel 20 U/day intramuscularly (IM) and a prednisone placebo orally (PO) or prednisone 2 mg/kg/day PO and an Acthar Gel placebo IM, for 2 weeks. Acthar Gel and matching placebo were administered as a single dose/day. Prednisone and matching placebo were administered as 2/mg/kg/day.

If the patient responded to therapy within the first 2 weeks, the dosage of the drug was tapered to zero over a 1 to 2-week period. Then, the patient was monitored at 2 weeks and 6 weeks after discontinuation of therapy to substantiate a continued response.

If a patient did not respond after the first 2 weeks, therapy was continued (Acthar Gel 30 U/day or prednisone 2 mg/kg/day) for an additional 4 weeks, after which study drug was tapered to zero over a 2-week period.

Nonresponders to the initial 2 weeks of therapy or the additional 4 weeks of therapy were then crossed over to the other drug after a 1-week washout period, and the protocol was repeated. Patients who failed to respond to either Acthar Gel or prednisone were treated with clonazepam (0.03 to 0.18 mg/kg/day) over an 8-week period. Note that the so-called cross-over is not a typical cross-over design in the clinical trial. In this trial, the sponsor simply re-assigned the non-responders to the other treatment group. It did not involve all subjects in the trial.

The response to therapy was evaluated at specific times throughout the study by 24-hour video and polygraphic monitoring, developmental testing, and determination of serum cortisol concentrations.

3.1.3.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary response to therapy in this study was defined as total cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. Spasms and hypsarrhythmic EEG pattern were assessed by serial 24-hour video and polygraphic monitoring.

(2) Secondary Efficacy Endpoints

Secondary endpoints included EEG changes in nonresponders and changes in mental and developmental status.

Note that again the original publication (Hrachovy 1983) did not use primary and secondary endpoints.

3.1.3.4 Patient Disposition, Demographic and Baseline Characteristics

Twenty-four infants with IS and hypsarrhythmic EEG patterns were enrolled in the study; 12 were randomly assigned to Acthar Gel plus prednisone placebo and 12 were randomly assigned to prednisone and an Acthar Gel placebo.

Table 12 Summary of Patient Disposition by Treatment Group

	Acthar Gel N=12 n (%)	Prednisone N=12 n (%)	All Patients N=24 n (%)
Number of patients enrolled	12 (100.0)	12 (100.0)	24 (100.0)
Number of patients completed initial phase[a]	9 (75.0)	12 (100.0)	21 (87.5)
Number of patients in the crossover phase	4 (33.3)	8 (66.7)	12 (50.0)
Number of patients prematurely withdrew	3 (25.0)	0 (0.0)	3 (12.5)
Number of patients withdrew due to AEs	2 (16.7)	0 (0.0)	2 (8.3)
Number of patients withdrew due to death	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients withdrew due to other reason	1 (8.3)	0 (0.0)	1 (4.2)

[Source: Sponsor's clinical study report 222017-04 Table 10.1, confirmed by the reviewer]

The median age of all patients is 8.20 months (range: 3.5 to 24.4 months) at start of treatment. More patients are female (14/24, 58.3%) than male (10/24, 41.7%). Most patients are White (15/24, 62.5%). The majority of patients had symptomatic etiology of IS (19/24, 79.2%); 8 patients (8/24, 66.7%) were symptomatic in the Acthar Gel group and 11 patients (11/24, 91.7%) were symptomatic in the prednisone group.

3.1.3.5 Sponsor's Primary Efficacy Results

There is no difference in overall response rate between Acthar Gel and prednisone in patients who were non-responders in the initial phase of the study and who received these treatments as alternative therapy in the crossover phase of the study.

Table 13 Analysis of Response to Treatment

Treatment Phase	Treatment	N	Treatment Response			*P*-value[a]
			EEG Responder	Clinical Spasms Responder	Overall Responder	
Initial	Acthar Gel	12	9 (75.0%)	5 (41.7)	5 (41.7)	>0.9999
	Prednisone	12	5 (41.7)	4 (33.3)	4 (33.3)	
Crossover[b]	Acthar Gel	8	3 (37.5)	4 (50.0)	3 (37.5)	>0.9999
	Prednisone	7	4 (57.1)	3 (42.9)	3 (42.9)	
Final[c]	Acthar Gel	13	8 (61.5)	9 (69.2)	8 (61.5)	ND[d]
	Prednisone	11	8 (72.7)	7 (63.6)	7 (63.6)	

a. *P*-value based on the 2-sided Fisher's exact test for treatment effect on overall response rate.
b. Crossover was conditional, including only patients did not respond to initial treatment.
c. Count based on each patient's last treatment. If patient did not crossover to another treatment then final treatment was the initial treatment, if a patient did crossover then crossover treatment was the final treatment
d. Not done because final treatment was not randomly assigned but a mix of initial treatment randomization and crossover conditional on initial treatment response.

[Source: Sponsor's clinical study report 222017-04 Table 11.1]

3.1.3.6 Sponsor's Secondary Efficacy Results

There does not appear to be a relationship between treatment or treatment response and change in mental and developmental status. Complete disappearance of the hypsarrhythmic EEG pattern was reported in 1 nonresponder (1/9, 11.1%).

The sponsor argued that the trial was under powered to show a meaningful treatment difference.

3.1.3.7 Reviewer's Results

The reviewer is able to confirm the results reported by the sponsor.

Note that the so-called cross-over is not a typical cross-over design in the clinical trial. In this trial, the sponsor simply re-assigned the non-responders to the other treatment group. It did not involve all subjects in the trial. The reviewer would focus only on the initial stage as the result is much easier to interpret.

3.1.3.8 Conclusions

The sponsor argued that this study evaluated a dose that is below that being recommended by Questco. The overall response rates seen in these analyses to both Acthar low-dose and prednisone are similar between the 2 treatments. Again, the sample size is small and the efficacy data are limited. The results can be due to the small sample size or due to ineffectiveness of the low dose ACTH. Conclusion on efficacy of ACTH cannot be drawn based on this trial.

3.2 Evaluation of Safety

Please refer to the clinical review for safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Due to small number of patients enrolled in each of the trial, it is hard to reach any conclusion based on subgroup analyses. The reviewer provided summary statistics for each study.

Please refer to Table 3 for subgroup analysis by age in Study 222017-01. Table 14 shows the number of overall responses in each gender. Ethnicity information is not available in Study 222017-01.

Table 14 Summary of Overall Responses by Gender in Study 222017-01

	Acthar Gel		Prednisone	
Gender	N	responses	N	Responses
female	11	9	6	1
male	4	4	8	3

Table 15 Summary of Overall Responses by Subgroups in Study 222017-05

	Acthar High Dose		Acthar Low Dose	
	N*	Responses	N	Responses
White	10	6	11	4
Other	17	9	13	8
Female	14	5	8	4
Male	14	10	19	9
Age>7 month	16	9	13	7
Age<=7 month	12	6	14	6

* Total number of patients may not add up across subgroups due to some missing information

Subgroup analyses in study 222017-04 are based on initial stage before non-responders were crossed over to the other treatment group.

Table 16 Summary of Responses by Subgroups in Study 222017-04

	Acthar		Prednisone	
	N	Responses	N	Responses
White	7	3	8	2
Other	5	2	4	2
Female	7	3	7	3
Male	5	2	5	1
Age>7 month	7	3	9	3
Age<=7 month	5	2	3	1

4.2 Other Subgroup Populations

Other subgroup analyses are not performed in this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Unlike the conventional pivotal trials submitted for drug approvals, the efficacy evidence of Acthar gel in treating infantile spasms is based on three published randomized controlled trials. Although the sponsor obtained the source efficacy data of those three trials and re-analyzed them, there was no prospectively defined statistical analysis plan. The sample size of each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. Therefore the efficacy data to draw conclusions are limited. Even though the sponsor used one study (222017-04) as the pivotal trial and the other two as supportive trials, this was not determined prospectively. All three studies should be weighted carefully. Furthermore, the so-called primary endpoint may not carry as much weight as the primary endpoint in the conventional clinical trials since it was not defined prospectively.

Study 222017-05 had a number of patients who did not complete the treatment protocol. Depending on the population used for analyses, the conclusion can vary. The analyses of overall response and EEG response showed no statistically significant differences between the 2 treatment groups. The analysis of the spasm control response by IS etiology showed a nominally significant difference between the Acthar high-dose and Acthar low-dose treatment groups in

favor of Acthar high-dose. This is based on the sponsor-defined mITT population. The significance disappeared if some other defined population is used (e.g., ITT population, completed patients population). Study 222017-04 showed similar overall response rate in both Acthar low-dose group and prednisone group. It cannot be determined whether it suggests that the low dose Acthar has similar effect in treatment infantile spasms as prednisone, or it is likely due to the small sample size of the trial.

The reviewer compared response rates across all three trials for consistency (Table 11). While the response rates in prednisone group and in ACTH low dose group vary in different trials, the response rates in ACTH high dose group differ the most across trials. The response rate in ACTH high dose group is much lower in Study 222017-05 than in Study 222017-01.

5.2 Conclusions and Recommendations

The sponsor obtained source efficacy data from three published, randomized, controlled studies. Among three studies, Study 222017-01 showed that Acthar Gel was significantly better than prednisone in both EEG response and clinical seizure response as well as the overall response ($p<0.01$). Study 222017-05 had 59 patients enrolled in the trial but a number of patients did not complete the study protocol, which had a considerable impact on the results of the trial. Depending on the population used for analyses, the conclusion can vary. Study 222017-04 compared Acthar low-dose with prednisone and showed that the low dose did not differ much from prednisone numerically ($p>0.99$).

Even though Study 222017-01 showed highly significant treatment effect of Acthar Gel, it is somewhat concerning that the conclusion cannot be directly confirmed in the other two trials. The analyses are retrospective and the sample size in each trial is small. With such small sample size, the study sample may not be a good representation of the intended pediatric population. The data to draw a definitive conclusion are limited. The efficacy evidence from three trials needs to be weighted carefully.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22432	ORIG-1	QUESTCOR PHARMACEUTICALS INC	H.P.ACTHAR GEL (Repository Corticotropin Injection)

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/s/

JIALU ZHANG
04/02/2010

KUN JIN
04/02/2010
I concur with this review.

KOOROS MAHJOOB
04/05/2010
I read this review and I discussed my views with the reviewer. My views are incorporated in this final version and I concur with that.

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